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Science Focus
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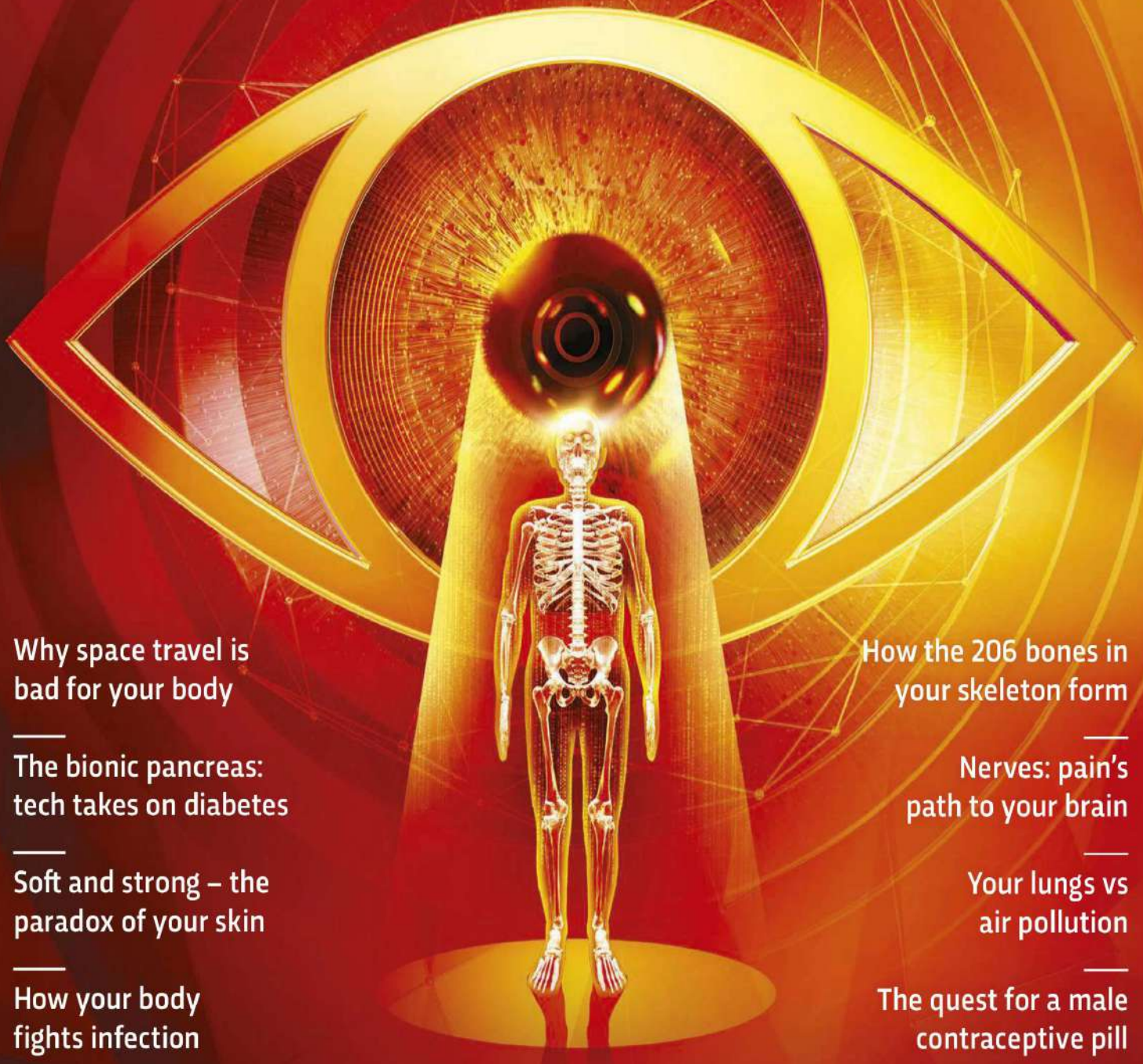
VOL.17

A SCIENTIFIC GUIDE TO THE
HUMAN BODY



Why space travel is bad for your body

The bionic pancreas: tech takes on diabetes

Soft and strong – the paradox of your skin

How your body fights infection

How the 206 bones in your skeleton form

Nerves: pain's path to your brain

Your lungs vs air pollution

The quest for a male contraceptive pill

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You're amazing

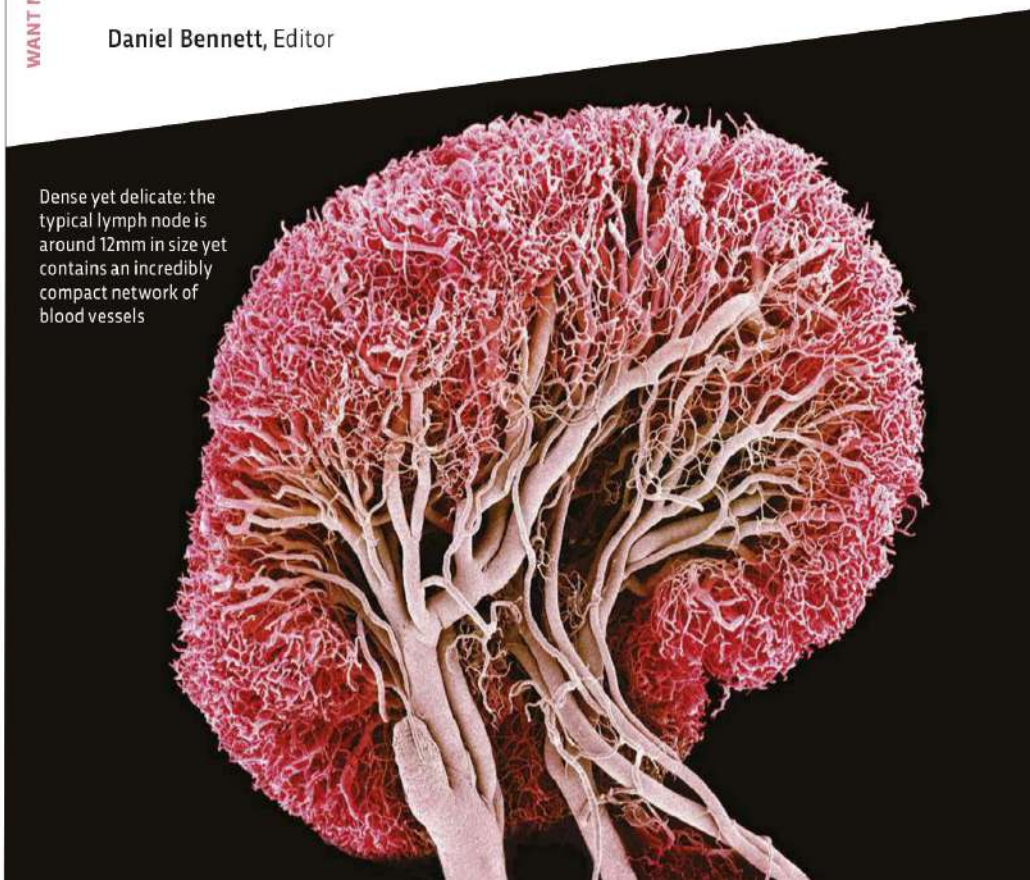
From a purely numerical perspective, your body is amazing. To give you just a few examples of exactly how amazing, consider the following: there are 206 bones in your skeleton, more than half of which are found in your hands and feet; there are around 100,000km of vessels threaded around you that carry blood to every organ and extremity; and there are a staggering 39 trillion microbial bacteria, fungi and virus cells living on and in you that contribute to everything from digesting food and fighting off infections, to how well you sleep and how much you weigh.

What's perhaps more amazing, though, is the fact that these and all the other numerous elements that combine to make your body are able to integrate and function so well together. Especially when the whole ensemble is so finely tuned – your body has an optimal operating temperature range of just 2°C and your heart pumps blood through your entire network at less than 2psi. What other machine can you think of that has anything like the number of parts and level of precision found inside the human body, yet is expected to operate continuously for decades without suffering any major malfunctions?

These are just a few of the astonishing attributes of the human body that made us want to find out more about it. To that end, we enlisted expert help from a range of doctors and writers who specialise in explaining exactly how the various systems of your body work and what you can do to keep them working. After all, you're amazing and we want to help you stay that way.

Daniel Bennett

Daniel Bennett, Editor



Dense yet delicate: the typical lymph node is around 12mm in size yet contains an incredibly compact network of blood vessels

CONTE

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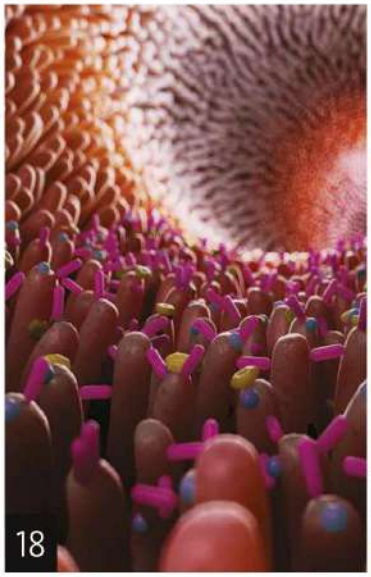

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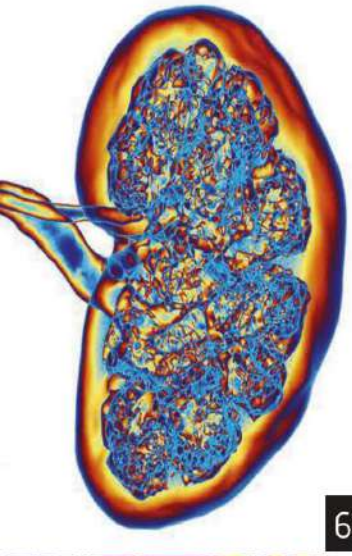
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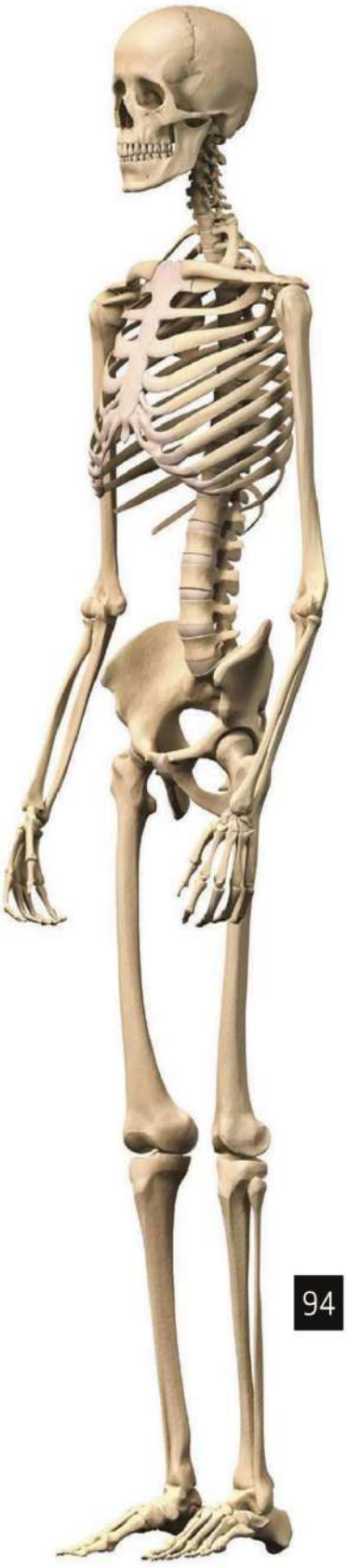
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Circulatory SYSTEM

You need air to breathe and food to eat, but neither would do you any good if they couldn't be transported around your body. If it wasn't for your circulatory system constantly pumping your blood, and all the oxygen and minerals contained within it, through the network of veins that run from your head to your toes, you'd run into serious trouble very quickly

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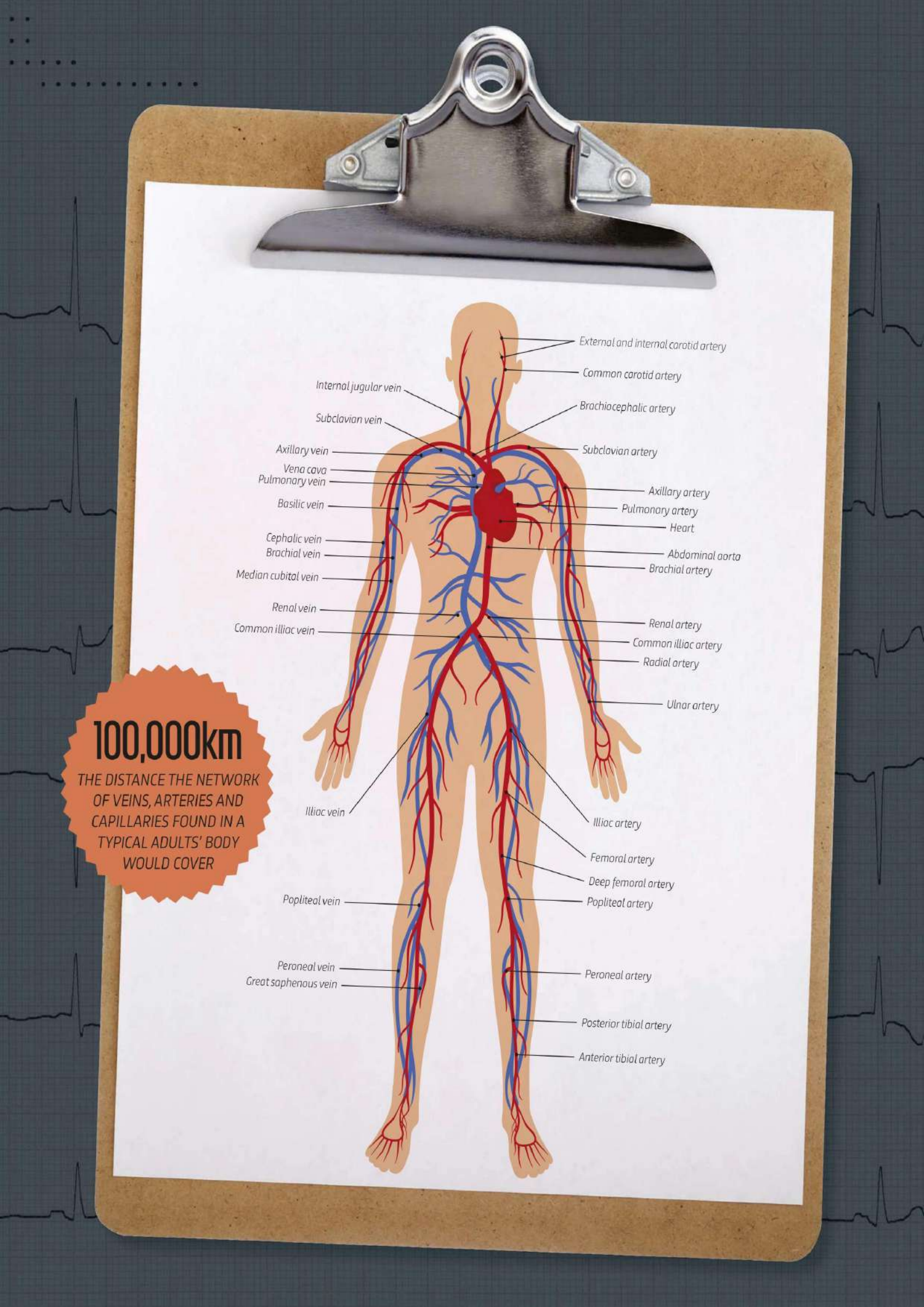
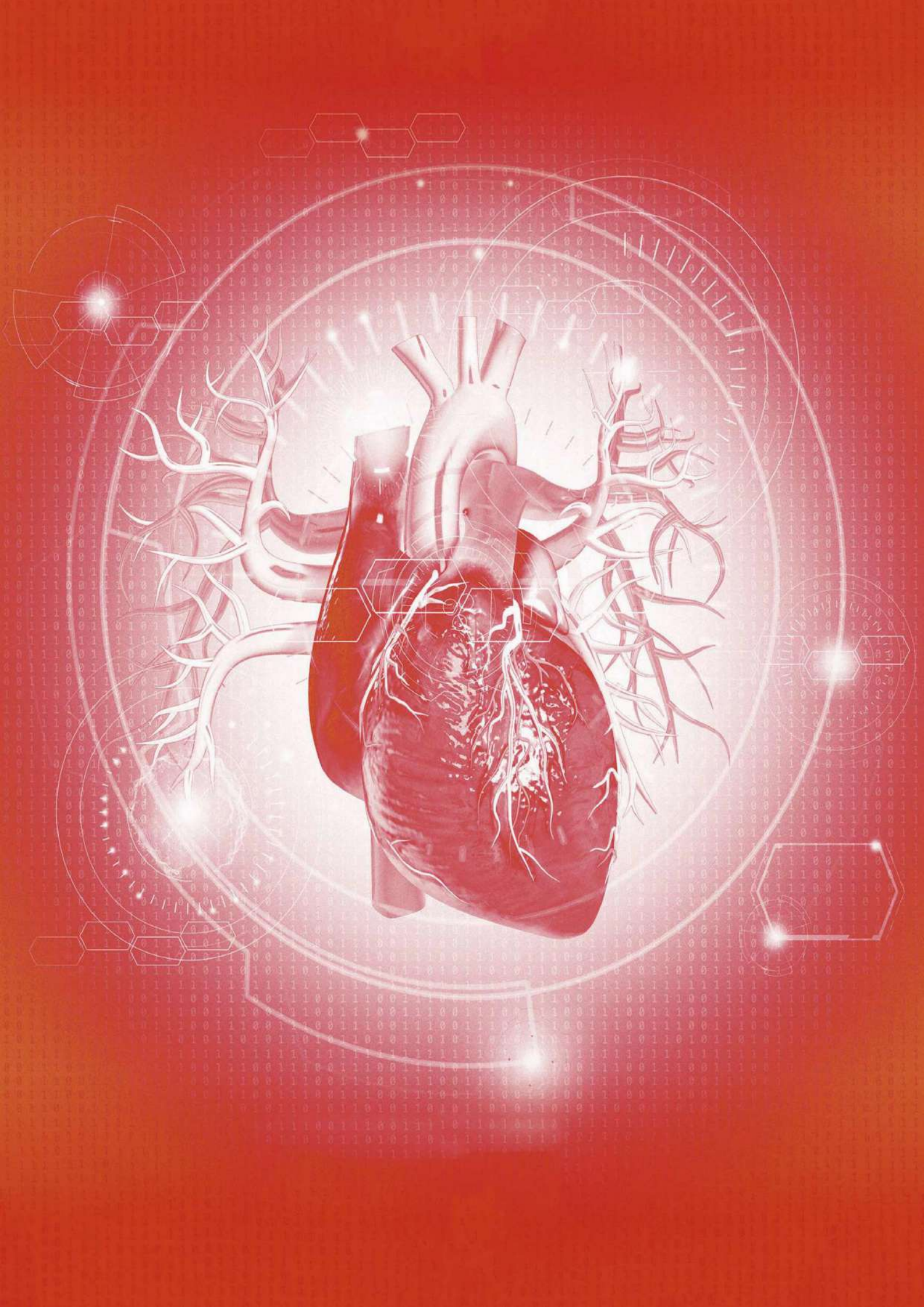

External and internal carotid artery
Common carotid artery
Internal jugular vein
Brachiocephalic artery
Subclavian vein
Subclavian artery
Axillary vein
Vena cava
Pulmonary vein
Axillary artery
Pulmonary artery
Basilic vein
Heart
Cephalic vein
Abdominal aorta
Brachial vein
Brachial artery
Median cubital vein
Renal vein
Renal artery
Common iliac vein
Common iliac artery
Radial artery
Ulnar artery
Iliac vein
Iliac artery
Femoral artery
Deep femoral artery
Popliteal vein
Popliteal artery
Peroneal vein
Great saphenous vein
Peroneal artery
Posterior tibial artery
Anterior tibial artery
100,000km
THE DISTANCE THE NETWORK OF VEINS, ARTERIES AND CAPILLARIES FOUND IN A TYPICAL ADULTS' BODY WOULD COVER



HEART OF THE MATTER

Keeping blood circulating around the network of vessels and organs in your body is a 24/7 job. And there's one four-chambered bundle of muscle and nerves at the heart of the entire operation...

words by SIMON CROMPTON

Heart specialists like the term 'perfuse'. It's a word that sums up the role of the circulatory system – the heart and its approximately 100,000km network of veins, arteries and capillaries that carry blood to virtually every cell in your body. The system perfuses each organ in blood, supplying just the right amount of oxygen, nutrients and regulatory hormones to keep it healthy.

At the same time, the circulatory system takes away carbon dioxide and waste products that would otherwise harm cells. It also regulates your body's temperature and transports your white blood cells around your body so they're where they are needed to fight infection.

If you imagine the circulatory system as a simple pump with tubes, think again. "The circulatory system is a fantastically sophisticated machine," says Barbara Casadei, Professor of Cardiovascular Medicine at the British Heart Foundation's Centre of Research Excellence, University of Oxford. "After nearly 30 years in cardiology, I still find it amazing that it can selectively perfuse each organ according to its needs at the time, yet still maintain blood pressure in the whole system."

A SELF-AWARE SYSTEM

Your circulatory system (also known as the cardiovascular system) consists of: your heart, the arteries that take oxygenated blood from your heart, the veins that bring deoxygenated blood back to your heart, and the tiny blood vessels called capillaries that branch off arteries and veins – feeding (and taking waste products from) every cell in your body.

But it's not a simple circular system. Your heart is, in effect, two pumps joined together, each powering separate but ➤

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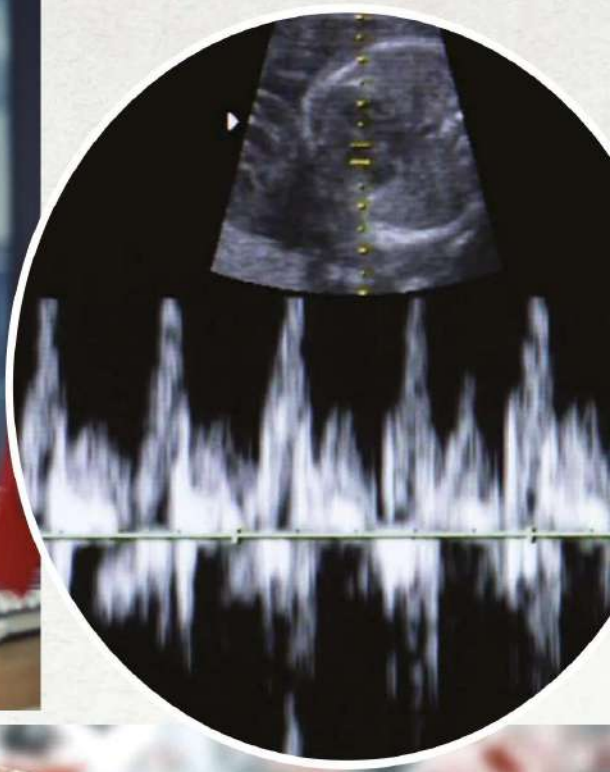
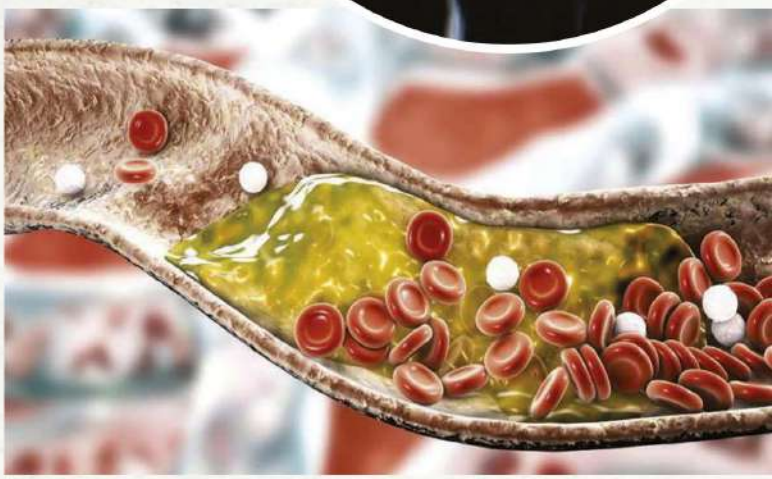




Your heart started beating 22 days after you were conceived and will continue to do so for your entire life

linked circuits. One circuit feeds deoxygenated blood to your lungs to get rid of waste carbon dioxide and pick up oxygen. The other pumps this oxygenated blood all around your body.

On the way around your body, blood passes through the gut where it picks up nutrients to feed organs, through the kidneys and liver where waste products are filtered out, and is then carried on to the brain, which demands large amounts of oxygen and nutrients.

What's remarkable is the way the flow is regulated. Your heart needs to pump hard and maintain a good blood pressure, so that plenty of blood reaches your brain even when you're standing and gravity is pushing it to your toes. But too hard a flow would cause damage to your blood vessels and delicate tissues, particularly the brain.

So your veins have valves to prevent backward flow and your capillaries dilate and contract to divert flow to areas where blood is most needed. If you're running, for example, blood will be diverted away from your digestive organs and towards your leg muscles. Receptors throughout the system act as sensors, detecting blood pressure and chemical changes in the blood, which are translated into nerve and hormone signals that, in turn, control how wide your blood vessels open and how fast your heart beats.

"It's a wonderful complex system, so it's not surprising that if something goes wrong, we are in serious trouble," says Prof Casadei.

UNDER PRESSURE

As your blood moves around your body it pushes against the sides of blood vessels. This pressure is a product of both how narrow your blood vessels are and how hard your heart is working. You can run into problems if your blood pressure is too high or too low so it good to get it tested occasionally. A blood pressure test provides two readings. One is the pressure when your heart is pushing blood into the arteries (systolic pressure) and one is in the instant between

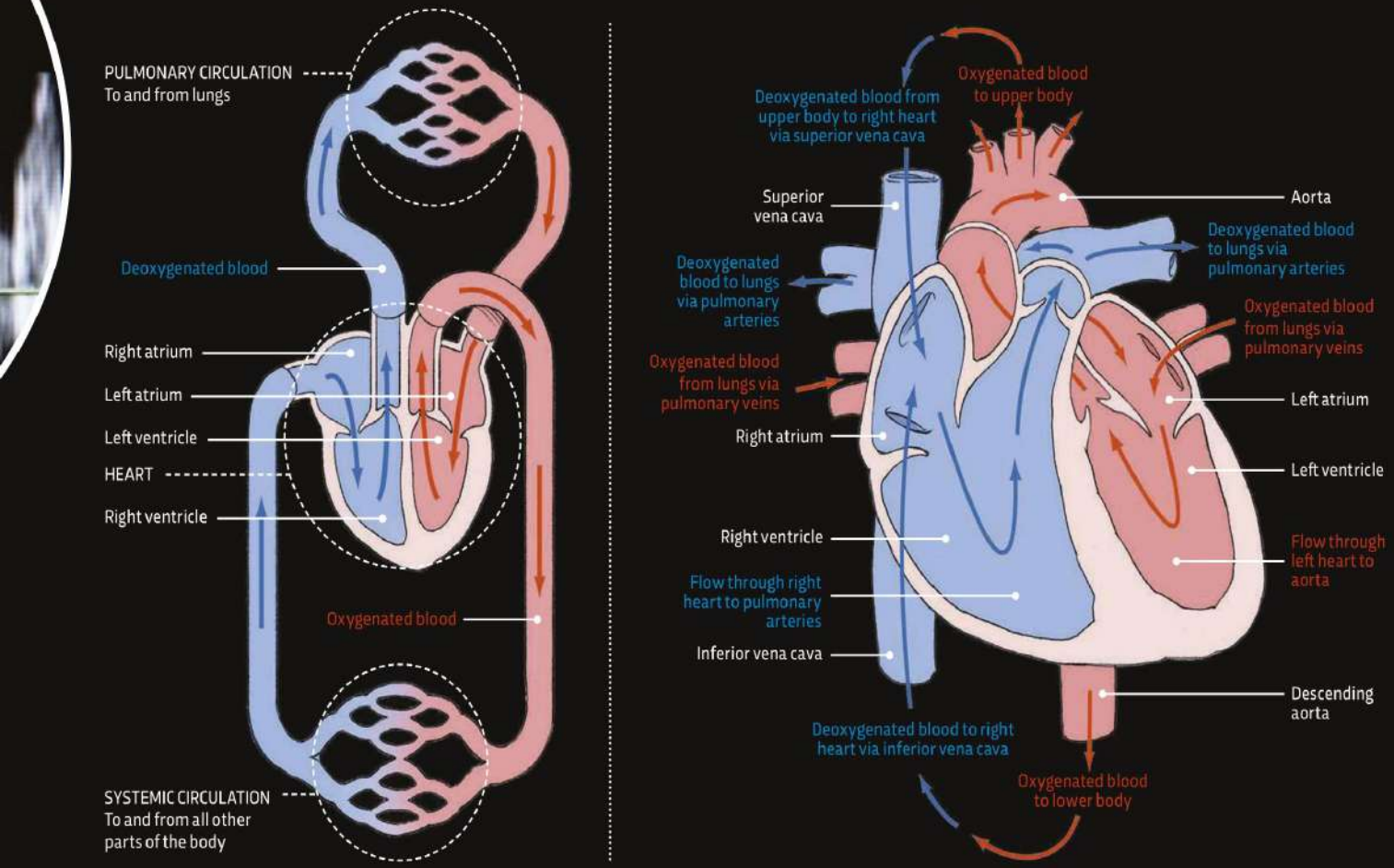
TOP LEFT: Your blood pressure provides an indication of the condition of your circulatory system

TOP: Ultrasound scans are used to check on the heart beat of babies as they develop in the womb

ABOVE: Atherosclerosis, the accumulation of fatty plaque in your arteries, is a common cause of heart attacks and strokes

CIRCULATORY SYSTEM AND HEART ANATOMY

How the four chambers of your heart work in sequence to pump blood to your lungs and then on to the rest of your body



beats, when the heart chambers fill with blood (diastolic pressure).

Together, these two readings provide an indication of how much strain is being put on your heart and blood vessels. According to NHS guidance, an ideal blood pressure is between 90/60 millimeters of mercury, or mmHg, and 120/80mmHg (the figure before the stroke is systolic, the figure after is diastolic). High blood pressure is considered to be 140/90mmHg or above. According to Blood Pressure UK, the systolic reading (first figure) is the most important, because it gives a better idea of your risk of suffering a heart attack or stroke.

To get an idea of how finely tuned your circulatory system is consider that the typical household plumbing system works on a pressure somewhere between 35-60 pounds per inch^2 (psi). One psi is equal to 51.1mmHg.

High blood pressure can cause problems because your blood vessels aren't just rigid tubes – they contain muscle to control expansion and contraction, and a protective lining that's just one cell thick (the endothelium).

If your blood pressure is too high, the muscles in the artery wall keep resisting it, which makes the muscles bigger and the artery walls thicker. This narrows the space in the arteries and leaves less room for the blood to flow through, increasing pressure even further and making blockages more likely. It also makes blood vessels more likely to rupture under the strain – and the result, for example in a stroke, can be catastrophic.

High blood pressure also damages the delicate endothelium. This makes blood vessels more vulnerable to inflammation and the process of atherosclerosis – the build-up of fatty plaques that can lead to heart attacks.

YOUR BEATING HEART

Your heart is a fist-sized muscle, containing four chambers that suck blood in and push blood out as they expand and contract. It started ➔

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EAT WELL AND EXERCISE

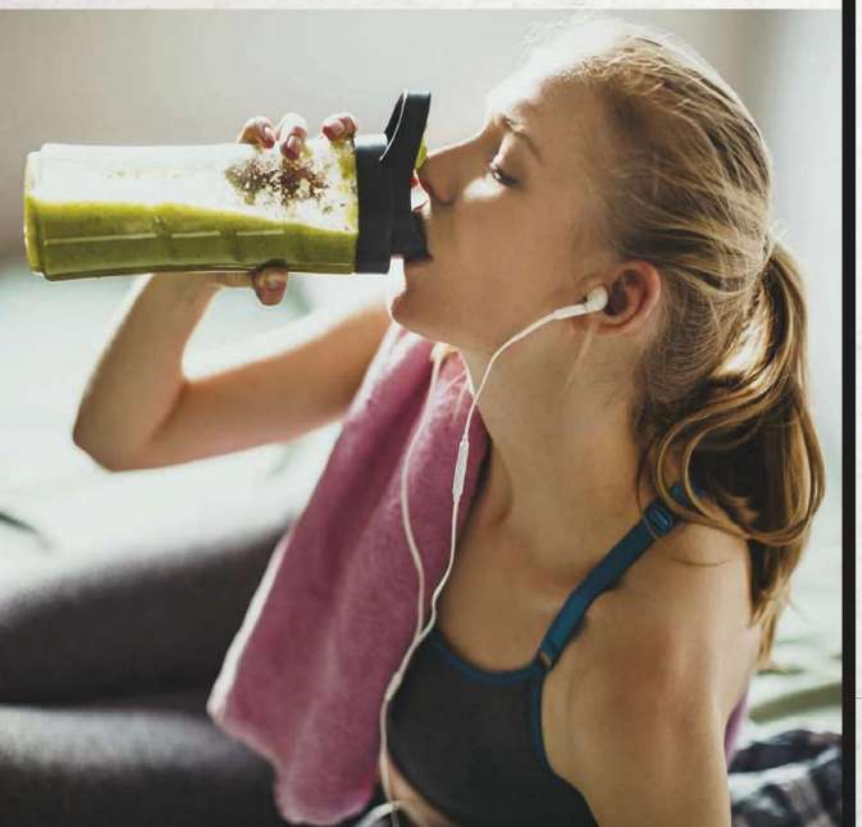
You can't beat your genes but you can mitigate their potential to create problems for you with the right lifestyle choices

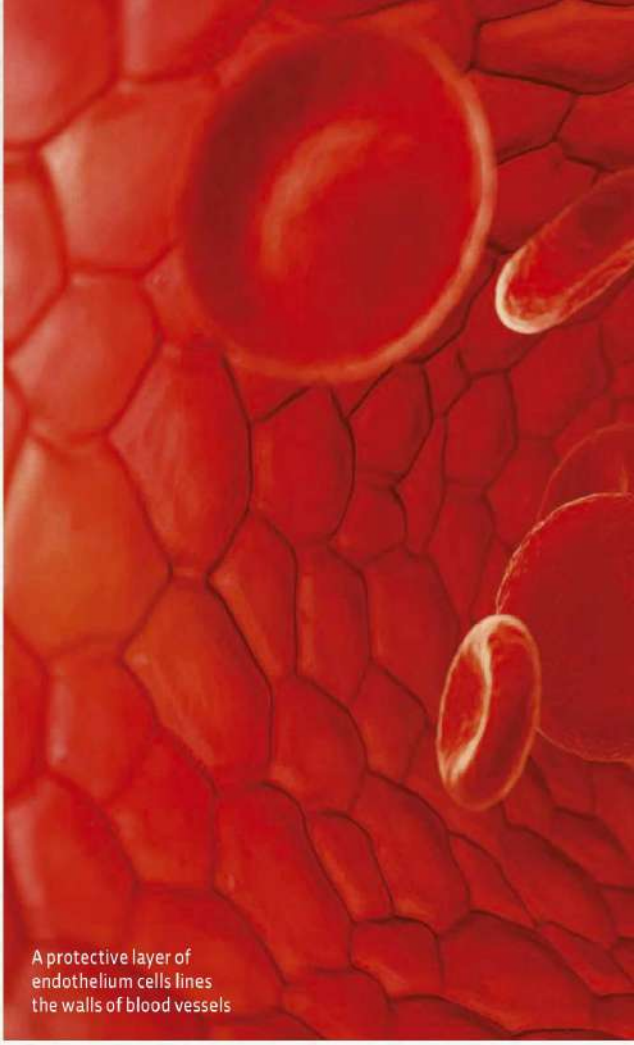
Many factors make you more likely to develop a build-up of fatty atheroma in your blood vessels, increasing your risk of heart attack – smoking, high cholesterol, inactivity, being overweight, high blood pressure, diabetes, your family history and your ethnic background.

Some people are born with a predisposition to high blood cholesterol, or greater inflammation in the blood vessels, which have been linked to a higher risk of cardiovascular disease. But while you can't do much about your genetics and the role they play in your chances of getting heart disease, you can do a lot about the lifestyle factors on the list: which is why you're told to look after your heart by not smoking, eating sensibly and getting enough exercise so often.

Though the precise ways in which diet has an effect on atheroma are debated, the advice from the British Heart Foundation is clear enough: eat a balanced diet that includes five portions of fruit and veg a day, and choose foods and drinks that are lower in fat, salt and sugar when you can.

Exercise is important because it conditions the muscles in your heart and blood vessels to perform, according to Prof Barbara Casadei. "It's difficult to pinpoint the exact way that exercise has an effect," she says. "But we do know that by increasing the rate of blood flow, you also encourage the growth of blood vessels called collaterals from your heart arteries, and that improves the total blood flow to heart muscle."





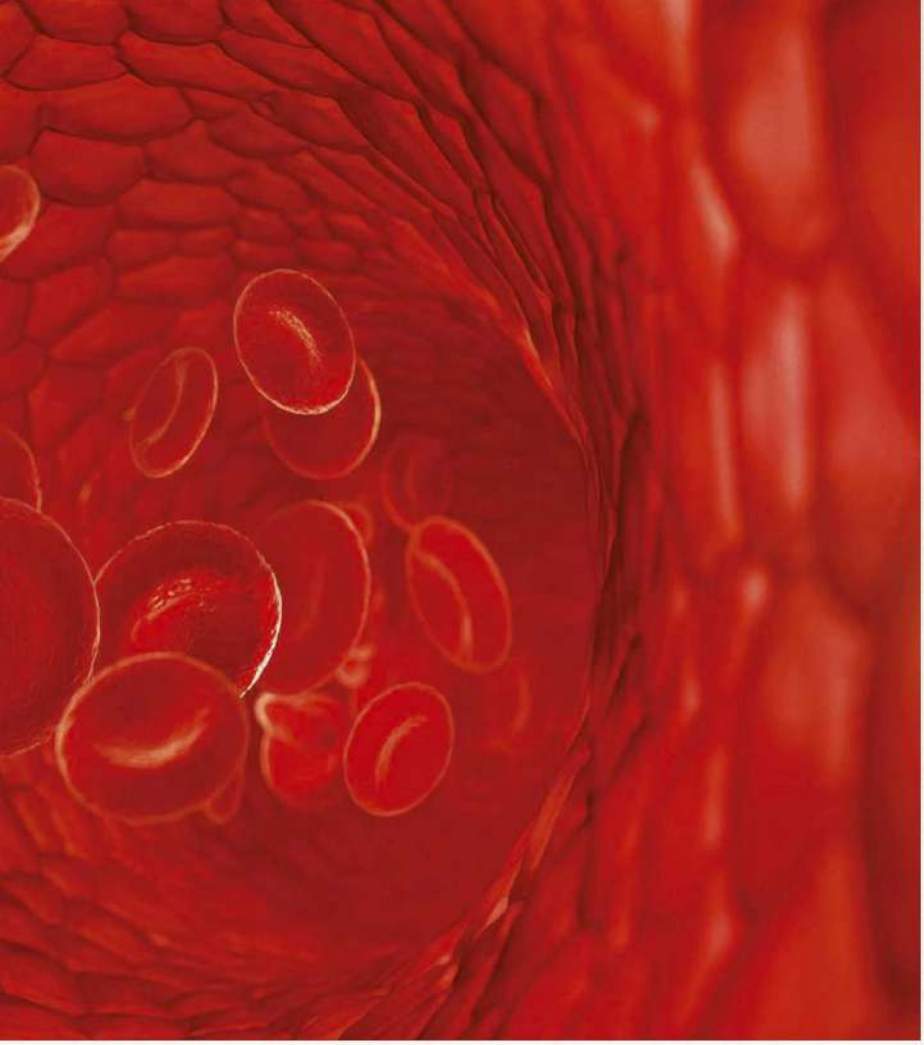
A protective layer of endothelium cells lines the walls of blood vessels

beating 22 days after you were conceived and will continue to do so for your entire life, at a typical rate of 60 to 100 times a minute. It beats 100,000 times each day, pumping 2,000 gallons of blood every 24 hours.

Four valves inside your heart ensure that the blood moves in the right direction. Deoxygenated blood from your body flows into the chambers on the right side of the heart and is pumped out to your lungs to pick up oxygen. Oxygenated blood then flows back from the lungs to the chambers on left side of your heart, which then pump bright red oxygenated body around the rest of your body.

All this happens in a heartbeat – a strong rippling contraction (pushing out blood) and expansion (refilling with blood) of the heart muscle – with the timing of each chamber contraction and valve opening coordinated by a sequence of electrical signals to the heart muscle. These signals come from a natural pacemaker called the sinoatrial node located in the right upper chamber (atrium) of your heart, which acts like a spark plug sending a charge through the electrical wiring of the chambers.

Your heart's role isn't just to pump blood, though. It also regulates the amount of fluid in



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Even a minor heart attack, where you remain conscious and breathing, needs immediate attention

the circulatory system by producing a hormone called atrial natriuretic peptide, which affects how widely blood vessels dilate and how much water and salt is excreted by your kidneys.

A BROKEN HEART

Like any complex system, the circulatory system can develop faults. Arrhythmias occur when the electrical signals that coordinate heartbeats don't fire properly causing irregular, fast or slow heartbeats. Disease or damage to the heart valves can impair blood flow through your heart. Some people inherit a heart muscle disease called cardiomyopathy in which the walls of the heart chambers become stretched, thickened or stiff making it more difficult for them to pump blood effectively.

But by far the most common life-threatening cardiovascular problems are caused by breakages and blockages in the blood vessels due to your genes, bad habits, wear and tear, high blood pressure and the build-up of fatty atherosclerotic plaques in arteries. Around 7.4 million people are living with heart and circulatory diseases in the UK, while heart attacks, strokes and other circulatory diseases are responsible for 28 per cent of all UK deaths.

Strokes are caused either by blood vessels rupturing, resulting in a bleed in the brain, or blockages stopping oxygenated blood reaching the brain. Heart attacks happen when one of the arteries that feeds heart muscle with oxygenated blood gets blocked, often due to a blood clot. As soon as heart muscle is starved of oxygen, it begins to die. This causes the symptoms of a heart attack. "The heart is full of nerves, so when there isn't enough oxygen getting to the muscle, it hurts," says Prof Casadei. "It's the same whether you have angina or a heart attack, though the intensity is different."

Dying heart muscle can no longer contract properly, leading to a reduction in cardiac output. Your heart's electrical impulses may also become irregular and uncoordinated (fibrillation) so it stops pumping altogether so your whole body is at risk of being starved of blood. That's when CPR (cardiopulmonary resuscitation) becomes critical. Someone, ideally a first aider, needs to keep compressing your chest and blowing air into your lungs to keep some oxygenated blood flowing around your body (particularly to your brain) until professional help arrives.

A defibrillator can help get your heart started again by effectively rebooting your heart. It delivers an electric shock that stops the abnormal beating patterns and allows the sinoatrial node to re-establish ordered impulses.

Even a minor heart attack, where you remain conscious and breathing, needs immediate attention because heart muscle cells can start to die after just 20 minutes without oxygen. Heart muscle cannot repair itself because it is made of 'terminally differentiated' cells, which can't divide and form new tissue. Once heart muscle is dead, it's dead. This is why heart researchers have long been interested in finding ways to regenerate heart tissue artificially. **SF**

Researchers have developed a 'pumping heart patch' – a net of stem cells to graft over the damaged area and support the process of regeneration

BREAKTHROUGHS

Fighting heart attacks

CPR and defibrillators may be the most familiar methods of dealing with heart attacks but a range of new techniques and medicines are in the process of being developed

1 CHOLESTEROL-BUSTERS

We know that heart attacks are linked to high levels of 'bad' LDL cholesterol in the bloodstream. Statins are one means of lowering blood cholesterol, and now a new class of cholesterol-busting drugs called PCSK9 inhibitors are available on the NHS. These are artificial antibodies that target and deactivate a protein in the liver, which, in turn, lowers the amount of LDL cholesterol in the bloodstream.

2 INFLAMMATION-BUSTERS

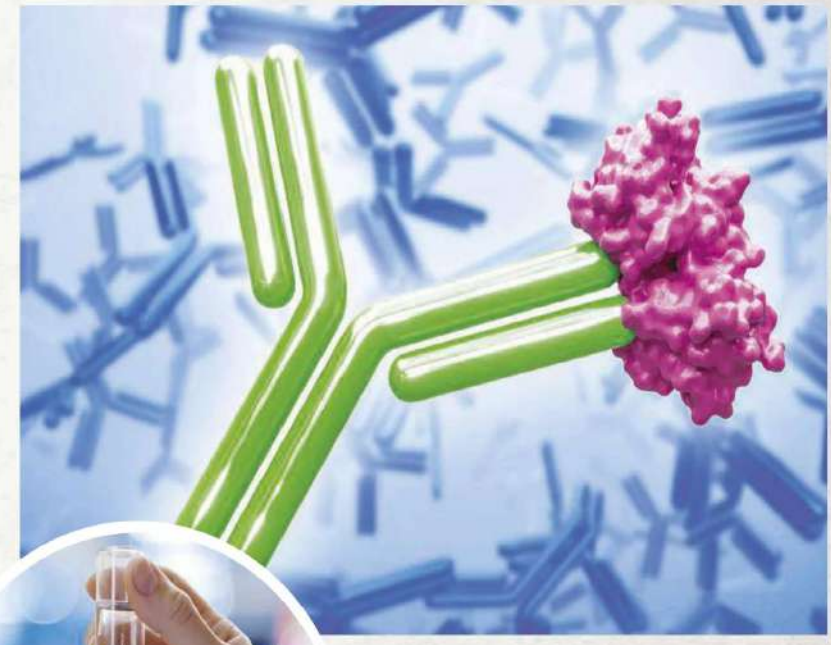
Research over the past decade has indicated that heart attack risk is linked to inflammation of the arteries. Drugs made of artificial antibodies (monoclonal antibodies) can reduce this inflammation. A large trial of one of these drugs, canakinumab, reported in 2017, found that the drug reduced the risk of heart attack by 24 per cent in people with heart disease. There have been concerns about developing this drug for general use because it is expensive and may increase the risk of infections, but the research opens the way for a new front of attack on heart disease.

3 ANTI-HEART ATTACK VACCINE

Research at Imperial College, London, has found that some of us are blessed with naturally occurring antibodies that are particularly good at neutralising harmful oxidised LDL cholesterol. The findings so far suggest they could protect against heart disease, raising the prospect of an antibody-based vaccine.

4 REGENERATION OF HEART TISSUE

How do you fix a broken heart? It's tricky because oxygen-deprived heart muscle cells die and don't come back after a heart attack, so hearts are left with inert patches of scar tissue. For many years, scientists have been trying to help heart tissue regenerate by implanting stem cells or young heart muscle cells cultured from stem cells into the heart. The problem is that they easily leak away and die, so Imperial College London researchers have developed a 'pumping heart patch' – a net of stem cells from the patient, grafted over the damaged area, and containing chemicals that will support the process of regeneration. Human trials are expected to begin in two years. **SF**



LEFT: A pair of pumping heart patches created by the team at Imperial College, London

TOP: An illustration of a PCSK9 inhibitor (green) bound to a PCSK9 molecule

ABOVE: Antibodies that can neutralise bad cholesterol could one day lead to a 'vaccination' to ward off heart attacks

by SIMON CROMPTON (@Simoncrompton2)
Simon is a science writer specialising in health, and formerly a medical editor on The Times.

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Digestive SYSTEM

Your digestive system's main role is to move, mix, break down, absorb and excrete everything you eat and drink. But it's more than just the passage food takes as it passes through your body. It's also home to a vast population of microorganisms that not only turn your meals into the minerals your body needs to function, but also influence everything from how you fight off illness to how well you sleep

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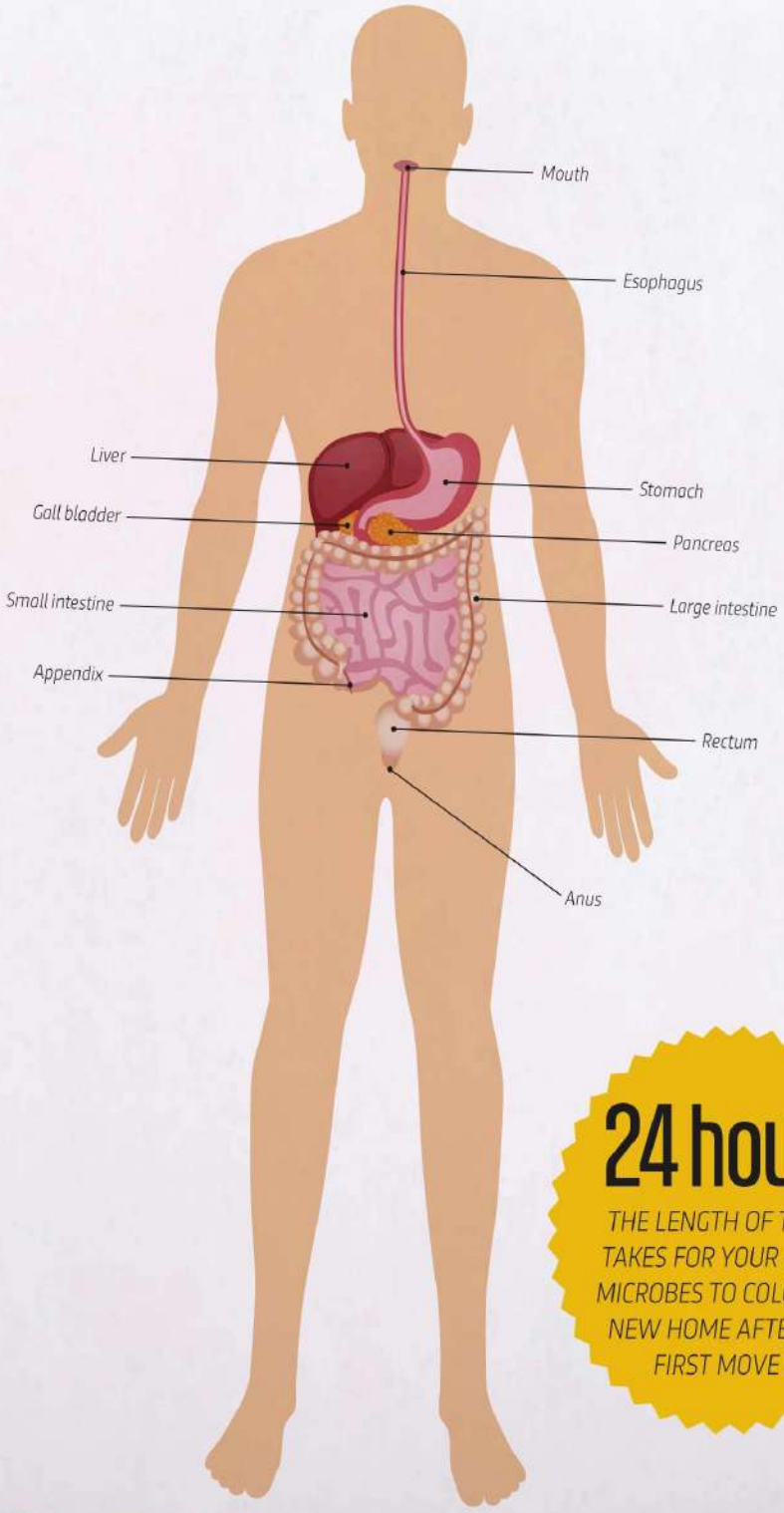

24 hours

THE LENGTH OF TIME IT TAKES FOR YOUR BODY'S MICROBES TO COLONISE A NEW HOME AFTER YOU FIRST MOVE IN

what is this?

We often think of bacteria and other microbes as 'bad'. But human bodies – and particularly our **DIGESTIVE SYSTEMS**, pictured here – teem with numerous species of tiny organisms that play an essential role in keeping us healthy and happy.

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We pick up the majority of our microbiome from our mothers when we are born

Gut reactions

Your digestive system is home to thousands of microscopic organisms that influence your daily life in more ways than you'd ever expect

words by MUN-KEAT LOOI

In any human body there are around 30 trillion human cells, but an estimated 39 trillion microbial cells including bacteria, viruses and fungi that live on and in you – mostly in your gut. Due to their small size, these organisms make up no more than about three per cent of your body mass, but they wield tremendous power.

You have around 20-25,000 genes in each of your cells, but your microbiome potentially holds 500 times more. Moreover, the ability of microbes to evolve quickly, swap genes, multiply and adapt to changing circumstances give them – and us, their hosts – remarkable abilities that we're only now beginning to fathom.

WHERE DO THEY LIVE?

Your body provides a broad range of environments, and microbes are capable of living in all of them. Each part of your body is a different type of ecosystem, like a planet with different continents and climates, the inhabitants of which have adapted to the characteristics of each location.

Your faces and hands are dry and cool. They're exposed to the elements, not to mention a constant stream of immigrant microbes every time you touch or come close to another thing. Nooks and crannies like your armpits have a lot to offer bacteria, being moist, warm and dark. The average human foot is even better, with 600 sweat glands per square centimetre – hundreds more than the armpits – that secrete a soup of salts, glucose, vitamins and amino acids, providing the perfect diet for a colony of bacteria.

Then there's your gut, where thousands of native bacteria live in partnership with you. They survive a hostile environment of darkness, high acidity and low oxygen, in what is a tumultuous river flushing through the stomach and intestines.

WHERE DO THESE MICROBES COME FROM?

Three-quarters of your microbiome can be traced back to your mother. The womb is a sterile place, free of microbes (at least we think so at the moment). But when you exit via the birth canal, you're bathed in vaginal microbes. This literal baptism of bacteria may be vital to a healthy start in life – babies who are born through caesarean section are more likely to develop allergies, asthma, coeliac disease and obesity later in life.

jargon buster

ANTIBIOTIC
This is a medicine that inhibits the growth of, or destroys, microorganisms. The antibiotics are actually produced by bacteria themselves as a form of survival (or, some scientists think, 'communication' between each other).

DYSBIOSIS
This is a disruption to the harmony of symbiosis, where the microbial community shifts in a way that harms its host. The phrase is often applied to the human gut microbiome, where it describes a condition caused by too few beneficial bacteria and an overgrowth of bad bacteria, yeast and/or parasites.

MICROBE
Single-celled organisms so tiny that millions can fit into the eye of a needle.

MICROBIOTA
A set of microscopic organisms. 'Microbiome' originally referred to their genomes – all the DNA of these organisms – but is now sometimes used in place of 'microbiota'.

PROBIOTIC
A substance that stimulates the growth of microorganisms.

SYMBIOSIS
This refers to the interaction between two different organisms living in close physical association, typically to the advantage of both.

You also ingest around a million microbes in every gram of food, and your diet has a direct impact on which species thrive in your gut microbiome. If you change diets, from meat-eater to vegetarian, for example, your gut bacteria changes accordingly.

Similarly, as you go through life, moving from one environment to another, you're exposed to microbes from different people and places. Every home has a distinctive microbiome that comes from the people who live in it. Just 24 hours after moving into a new home you'll have colonised it with your microbes. And anyone who grows up in a household with pets will be exposed to a far wider range of microbes, which is no bad thing. Scientists suspect that a lot of common modern allergies, such as hay fever, are triggered by an immune system that didn't learn to live with such microorganisms at an early age.

WHAT DO MY MICROBES DO?

Lots. In your gut, they control the storage of fat and assist in activating genes in cells involved with absorbing nutrients, breaking down toxins and creating blood vessels. They help to replenish the linings of your gut and skin, replacing damaged and dying cells with new ones.

Equally vital is their role in preventing illness. Your native microbes compete with invading ones, preventing them from getting a foothold. You're born with an immune defence system that's only partially formed. It's the interaction with microbes as you grow and develop that shapes it, influencing the classes of immune cells that are generated and the development of the organs that make and store them. As Ed Yong says in his book *I Contain Multitudes*, "The immune system is not innately hardwired to tell the difference between a harmless symbiont and a threatening pathogen... it's the microbe that makes that distinction clear."

In total, there are between 500 and 1,000 microbial species living in your gut

TOP: Your individual microbiome is so unique that you can be identified by the smell of one of your sweaty T-shirts

ABOVE: The human large intestine, seen here in yellow, is filled with many microbe species

Your microbiome even affects how you smell. Different microbe species might convert sweat into the smell of onions, or testosterone into the stink of urine, which act as strong signals for your friends and foes. These smells are highly personal: studies have found people can be identified just from their sweaty T-shirts.

Scientists also think that your microbiome may be a significant contributor to jet lag. The change in sleep patterns puts the rhythm of your gut bacteria out of sync with your behaviour, so different species are active at the wrong times. In fact, sleep is just one of the many ways through which microbes might affect your mood and behaviour.

Finally, your microbiome helps dispose of you in what's been dubbed the 'thanatomicrobiome'. After you die, the immune system stops working, leaving your microbes to spread freely. Your gut bacteria start digesting the intestines, and the surrounding tissues, from the inside out. Eventually they invade your capillaries and lymph nodes, spreading to your liver, spleen, heart and brain as they feed on the chemical cocktail that leaks out of damaged cells.

It's no surprise your gut microbiome is implicated in so much. Trillions of microbes live here, the majority of which are in the large intestine. Here, they help digest your food, releasing nutrients you otherwise wouldn't have access to. They produce vitamins and minerals, breaking down toxins and harmful chemicals. Your native *E. coli*, for example, makes vitamin K.

In total, there are between 500 and 1,000 microbial species living in your gut, including

GETTY IMAGES

A WHISTLESTOP TOUR OF HUMAN MICROBES

Say hello to the organisms that call your body home

MOUTH
Streptococcus mutans turns sugars into acid that erodes the enamel of your teeth, causing cavities.

SKIN
Propionibacterium acnes lives deep within your pores and hair follicles, and can cause spots.

GUT
The majority of your microbiome lives here, somewhere between 500-1,000 species.

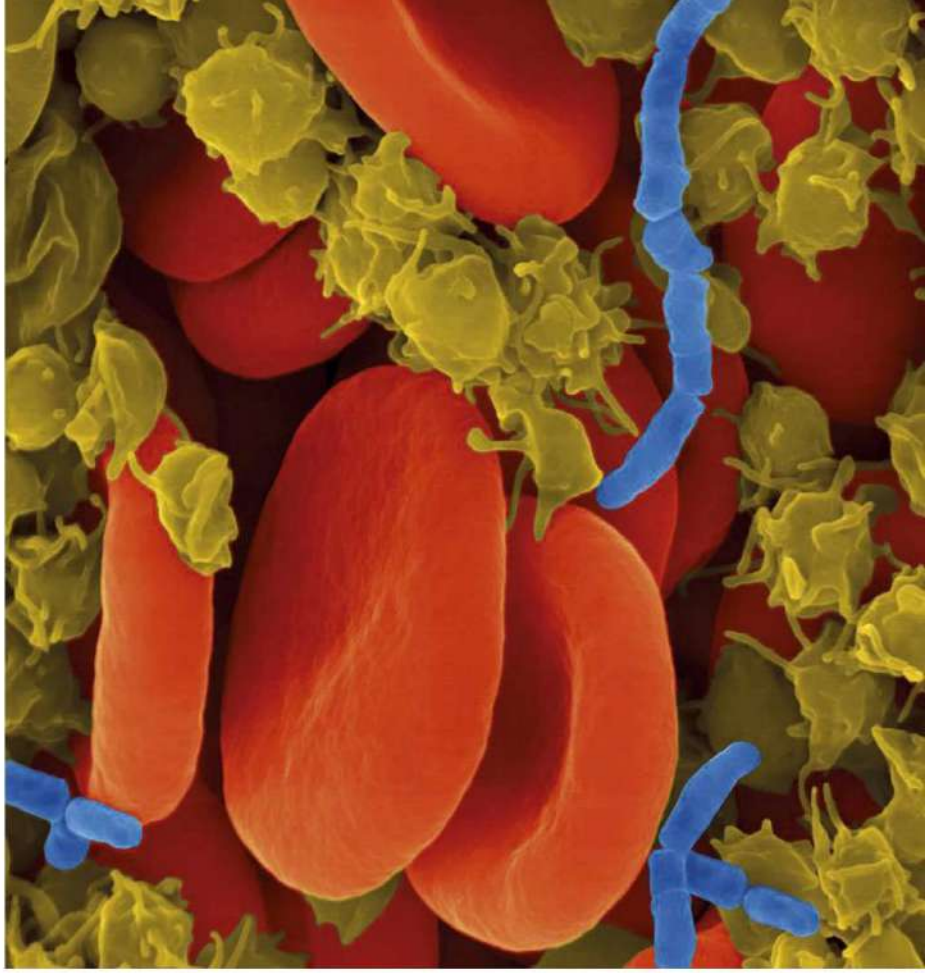
VAGINA
Dominated by one species, *Lactobacillus*. This bacteria pumps out lactic acid, keeping the vaginal environment at a low, acidic pH that discourages other bacteria, yeast and viruses from thriving.

SCALP
According to recent studies, dandruff is caused by the delicate balance of two common scalp bacteria: *Propionibacterium* and *Staphylococcus*.

ARMPIT
When some bacteria encounter sweat, they produce pungent compounds called thioalcohols. *Staphylococcus hominis* is one of the worst offenders.

POO
Given the huge numbers of microbes in the gut, it's no surprise that many find their way into your poo – an estimated 30 per cent of solid waste is dead bacteria.

FEET
The biggest cause of smelly feet might be *Staphylococcus epidermidis*, whose presence always seems to coincide with isovaleric acid – the smell of well-aged Stilton cheese.



Bifidobacterium bifidum, which makes lactic acid and acetic acid to help digest your food, and *Methanobrevibacter smithii* – not a bacteria but a separate kind of microbe called an archaea – that converts carbon dioxide and hydrogen gases into methane (the smelly component of farts). Your gut bacteria may also affect your weight by changing how much energy you extract from food. Different microbes favour different diets – some are good at breaking down plants, others fats.

In addition to releasing nutrients and regulating your immune system, your gut microbiome also balances hormone levels. The activity of microbes can stimulate cells in the gut to release large quantities of the neurotransmitter serotonin, which may affect signalling in the brain.

WHAT IF THINGS GO WRONG?

Generally, bad things happen when the balance of your gut microbiome is disrupted. At the simplest level, sickness can develop when normally harmless bacteria stray from their usual habitat. *Enterococcus faecalis* is part of the normal gut ecosystem. But if it gets into open cuts or your urinary tract, it can cause infections. Sepsis occurs when your gut microbes accidentally cross into your blood.

Your native gut bacteria can also interfere with medicines. Paracetamol is more effective for some people, thanks to their gut bacteria. And on the extreme end of the scale, the colon cancer drug Irinotecan can be turned toxic by some strains of gut bacteria. Meanwhile, Sulfasalazine, a drug for rheumatoid arthritis, only works if gut microbes convert it into an active state.

Obese people have different gut microbes to slimmer people, with research in mice indicating that transplanting bacteria can affect how much a mouse will eat (studies on people have been less conclusive).

Research over the past few decades has shown how stress – starvation, lack of sleep, separation from a parent, overcrowding, noise – can change the gut microbiome, at least in mice. Psychiatric and digestive problems often

WHAT WE STILL DON'T KNOW

1 CAUSE OR CONSEQUENCE

It's hard to tell if the microbiome is responsible for changes in diseases and behaviour, or if diseases and behaviour are responsible for the microbiome. Researchers are gradually piecing together how gut microbes influence the brain through the hormones and molecules they produce, but no one knows how important these are. Drug companies, keen to find new ways to treat neurological disorders, are investing money into research.

2 HOW DIFFERENT SPECIES RELATE

The interplay between different species of microbes is incredibly complicated and that's before you consider the influence of external factors. We know, for example, that the balance of two groups of bacteria – the Firmicutes and Bacteroidetes – affect obesity, but the link isn't clear enough to know how we might influence it. And even if we were to find a potential treatment, there's no telling if the body would accept it.

3 WHAT MAKES A HEALTHY MICROBIOME

How do you know if a microbiome is in disarray? Is a gut without a particular species unhealthy? And in comparison to what? Defining what is 'normal' or 'healthy' for a human microbiome is important, and this may differ widely between countries, regions, communities, cities and whether someone is young or old, rich or poor, outgoing or solitary. This is a further challenge to the dream of personalised medicines for everyone.

SCIENCE PHOTO LIBRARY X2

ABOVE LEFT: If your gut microbes (blue) stray into the bloodstream, they can cause infections such as sepsis

ABOVE: Bacterial infections of *C. difficile* (pictured) can be beaten by a faecal transplant

go together. Drinking lots of alcohol makes your gut leakier, allowing microbes to more readily influence your brain. And your gut microbiome gets less stable in old age.

All of these problems may be traceable back to a disruption of the natural microbial balance, what scientists call 'dysbiosis'. And once disrupted, it's not so easy to get it back into its balanced, stable state.

WOULD PROBIOTICS BENEFIT ME?

The idea is sound: by adding particular species of gut bacteria you can alter the balance of your microbial communities to provide health benefits. Yet commercially sold probiotics probably don't make much difference. Most contain perhaps a few hundred billion bacteria, 100 times fewer than naturally found in the gut. Plus, they are often not important members of the gut microbiome, and don't have what it takes to colonise and stay there for long enough to make a difference.

Where probiotics can be beneficial is after antibiotic treatments. Antibiotic medicines are weapons of mass destruction as far as your microbiome is concerned. One study conducted at the University of Valencia found that it took four weeks for the gut bacteria to re-establish themselves following a course of antibiotics, and certain bacteria did not reappear at all.

Once your microbiome is disrupted, it's not so easy to get it back into its balanced state

The right probiotics, chosen by a doctor, can help repopulate that ecosystem.

WHAT IS A FAECAL TRANSPLANT?

Exactly what it sounds like – taking a sample from someone else's poo and transplanting it into your body. And as gross as that sounds, it's actually very viable. Around 30 per cent of your poo is made up of gut bacteria, and transplanting the good bacteria from a healthy patient to a sick one could combat malicious infections, particularly those caused by bacteria such as *Clostridium difficile* and MRSA, which are resistant to most antibiotics. Faecal transplants have been used to treat hundreds of patients, more than 90 per cent of whom recovered from their illness. In a 2012 trial, faecal transplants cured 15 out of 16 *C. difficile*-infected patients, versus seven out of 26 with an antibiotic. As the results were so successful, the trial was halted and the antibiotic group was given faecal transplants.

IF MY MICROBIOME SUDDENLY DISAPPEARED, COULD I SURVIVE?

You might get by for a few weeks, possibly even years, but in the long run your health would suffer. You couldn't eat all the foods you normally would, because you couldn't break them down so wouldn't get enough energy and nutrients out of them. And you'd soon find yourself under attack from external microbes that suddenly don't have to compete with a native microbial army. Without our microbiome, it's arguable how 'successful' humans would be as a species. **SF**

by MUN-KEAT LOOI (@munkeatlooi)
is a science writer and editor.

Endocrine SYSTEM

A collection of glands, found in various locations around your body, serve as its communication and control network. This network – your endocrine system – uses chemical messages to regulate almost every aspect of your life, from your mood and metabolism, to your growth and ability to reproduce. Hormones, the chemical messages produced by the endocrine glands, therefore have a vital role to play in your health, but just how far their role extends is something scientists are still figuring out

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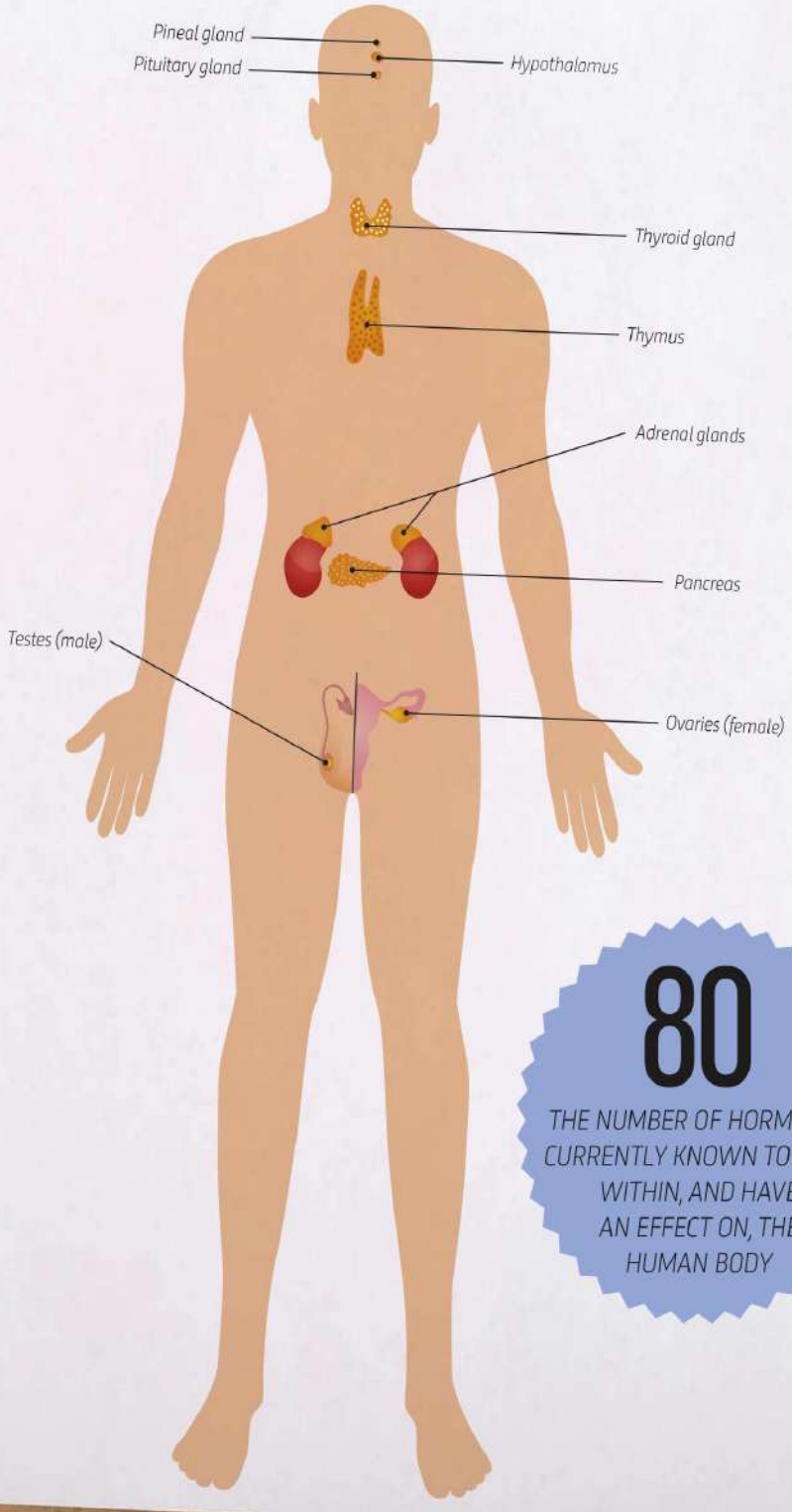

80

THE NUMBER OF HORMONES CURRENTLY KNOWN TO EXIST WITHIN, AND HAVE AN EFFECT ON, THE HUMAN BODY

THE DISCOVERY OF HORMONES

The chemicals produced by the endocrine system circulate through our blood, regulating our physiology and behaviour. But it took a long time for people to accept that hormones have such a big impact on our bodies

words by TOM IRELAND

Today, the word 'hormone' is commonly used and well understood. You might say you're feeling hormonal, or take hormones to prevent diabetes or pregnancy. Teenagers, especially, are known for being troubled by their 'raging' hormones. These amazing chemicals, secreted into your blood by your endocrine glands, control almost everything your body does – from your growth and development to your impulses and mood. There are even hormones that regulate your hormones.

Yet until the start of the 20th century, most scientists had no idea hormones even existed, let alone how they worked. The more visible systems of the body, such as the skeleton, muscles and major organs, had been known since ancient times. But hormones and the endocrine system were only just being found by anatomists by the 19th century, and their function remained a mystery for some time.

Despite this lack of understanding, humans have been unwittingly manipulating hormones in both animals and people for centuries. There is some evidence that ancient Chinese people were extracting hormones from urine for medicinal purposes as far back as 200 BC. In Italy from the 16th to the 18th centuries, opera singers known as castratos had their testicles removed before puberty to ensure their voices didn't drop. And for thousands of years, farmers have castrated male animals to reduce aggression.

Domenico Annibali was castrated as a youngster and became an international opera star in the 18th century

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WEIRD SCIENCE

It took a series of crude and controversial experiments in the Victorian era to kick-start the our understanding of the endocrine system and the hormones it produces. Over about 100 years, the emerging field of 'endocrinology' revolutionised science and medicine, and many common disorders of the endocrine system could suddenly be diagnosed and treated.

The story begins in 1849, with a German scientist called Arnold Berthold and several castrated cockerels. Berthold noticed that when young cockerels had their testes removed, in adulthood they failed to develop typically male characteristics, such as a large red comb and

what is this?

TESTOSTERONE, pictured here under a polarised light microscope, is mostly produced by the testes. Even before hormones were discovered, it was understood that removing the testes of youngsters would impact the development of adult male characteristics.

jargon buster

ADRENALINE
Adrenaline is one of the most familiar hormones and is famed for the 'buzz' it gives when released during frightening or exciting moments.

ENDOCRINE SYSTEM
Humans have at least 80 known hormones and 10 hormone-producing glands. The release of hormones, their effects, and their interaction with each other is known as the endocrine system.

HOMEOSTASIS
Hormones play a key role in the body's constant maintenance of a stable internal environment, known as homeostasis.

HORMONE
Hormones are chemicals released by the body to control processes including digestion, metabolism, respiration, sleep, reproduction, mood and growth, to name a few. They travel through the blood and bind to specific receptors on the target cell, triggering a change in cell function.

HPA AXIS
This stands for the hypothalamic-pituitary-adrenal axis, a complex system including the hypothalamus, the adrenal and pituitary glands, and many hormones.

The extravagant plummage and aggressive behaviour of cockerels is linked to their hormones

TOWARDS THE END OF THE 19TH CENTURY, THE STUDY OF TESTES AND THEIR FUNCTION WENT 'OFF-PISTE'

wattle. In what is now recognised as the first endocrinological experiment, Berthold transplanted severed testes back into the birds' bodies. The birds soon started to develop the traits of uncastrated cockerels, including the characteristic plumage and aggressive mating behaviour. The transplanted testes also redeveloped their own blood supply. The experiment suggested that whatever was causing the male characteristics was being emitted from the testes and going into the bloodstream.

Despite the significance of Berthold's findings, his results went largely unnoticed at the time – it would be another half a century before scientists progressed his ideas. Other scientists theorised that 'internal secretions' might be affecting the function of various organs, but they couldn't comprehend that chemicals in the blood could have such wide-ranging effects on the body.

Towards the end of the 19th century, the study of testicles and their functions went 'off-piste'. A physiologist called Charles-Édouard Brown-Séquard began a series of outlandish experiments, which involved injecting himself with liquid squeezed out of crushed animal testicles. In 1889, at the age of 72, he announced that he had reversed his own ageing by injecting the 'testicular juice' of dogs and guinea pigs.

The effects Brown-Séquard experienced were almost certainly placebo. His injections would have contained little testosterone and been quickly broken down by his body. Yet he claimed that almost any ailment could be cured by testicular juice. The news led to a fad for such injections, and by the end of 1889 thousands of physicians were administering them.

Fortunately, as more robust experiments with glandular extracts continued, endocrinology got back on track. In 1891, George Redmayne Murray announced he had managed to cure myxedema. Now recognised as untreated underactivity of the thyroid gland, the condition caused alarming swelling of the hands and eyes.

Murray's treatment involved injecting extracts from the thyroid glands of sheep. Like Brown-Séquard, he chopped up the animals' tissues and squeezed the juice out, before injecting it into his patients. Unlike Brown-Séquard's potions, Murray's extract did contain high levels of thyroid hormones.

It would be years before the thyroid's role in regulating metabolism and growth was understood, yet the treatment worked – making it the first effective application of endocrinology in conventional medicine.

By 1895 George Oliver and Edward Albert Schäfer had shown that injecting extracts of the adrenal and pituitary glands into animals raised their blood pressure. It was further proof that secretions released by glands could create important effects elsewhere in the body.

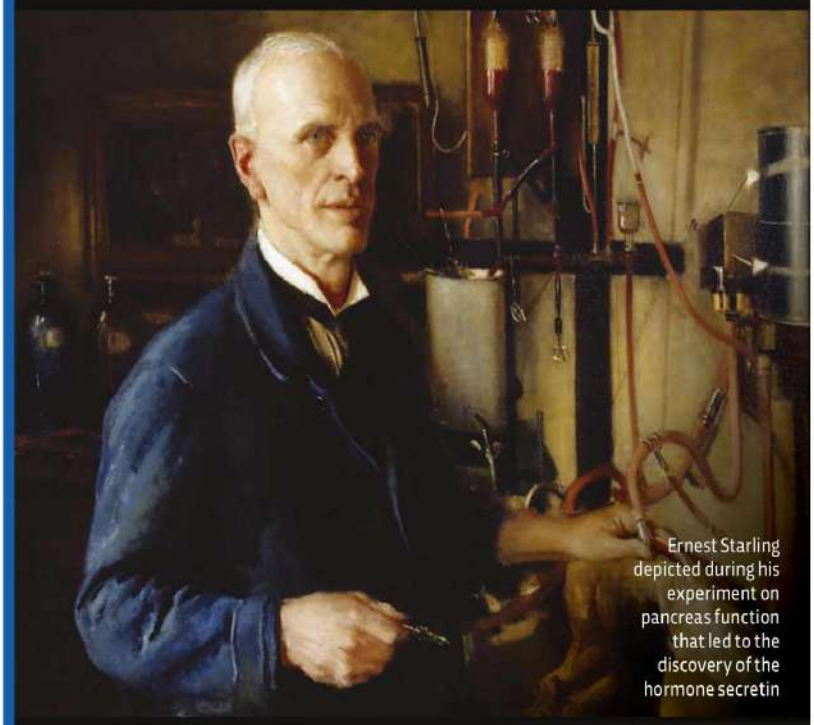
DARK PATHS

Despite mounting evidence of an internal chemical control system, the British Medical Association was reluctant to accept the idea. The prevailing wisdom was that the nervous system controlled the body's functions, and it was difficult for people to accept that this might not be the case.

This incomplete understanding led endocrinology down dark paths. In the early 1900s, thousands of men (including the poet WB Yeats) had a vasectomy-like procedure known as 'the Steinach' after the Austrian physiologist Eugen Steinach, who said tying off the testicles could reduce ageing and increase sexual vigour.

THE KEY EXPERIMENT

Ernest Starling and William Bayliss wanted to prove that hormones regulate the function of organs. While controversial, their experiments set endocrinology on the right path



Ernest Starling depicted during his experiment on pancreas function that led to the discovery of the hormone secretin

In 1902 Ernest Starling and William Bayliss were studying the nervous system's control of digestion at University College London. They were looking in particular at the duodenum – the part of the small intestine located immediately after the stomach. When gastric acid enters the duodenum, the pancreas releases pancreatic juice.

At the time, hormones were barely understood. A large number of scientists still thought that vital organ functions, such as the release of pancreatic juice, were controlled by the nervous system. To test this, Starling and Bayliss cut away all of the nerves in the pancreas and the duodenum of an anaesthetised dog. They found that pancreatic juice was still produced when acid passed through the duodenum.

They suspected that the duodenum was producing something that was entering the bloodstream and acting on the pancreas. To prove it, they scraped some tissue out of the duodenum, added acid, ground it up with sand, filtered the mixture and then injected it into the dog's blood. The dog's pancreas began to produce pancreatic juice almost immediately. Since there was a chance they did not dissect all of the nerves in the pancreas and duodenum, this second experiment proved it was an agent in the blood that stimulated the production of pancreatic juice, not nerves.

The pair called the substance released by the duodenum 'secretin' and later went on to find it in all vertebrates.

Tragically, from the late 1800s to the early 1900s, hundreds of thousands of healthy women had their ovaries removed, often by force, in the mistaken belief that it could prevent moodiness, hysteria, insanity and other conditions.

Thankfully, in 1902, a defining experiment was conducted by the physiologist Ernest Starling and his brother-in-law William Bayliss. The two were known to be compulsive experimenters and they proved that chemicals in the blood could change how an organ behaves independently of the nervous system.

Having become known for this work, Starling was invited to give a series of lectures to the Royal College of Physicians in 1905. Here, while describing the chemical agents he and his peers had been studying, he used a word he had made up the night before while dining with a scholar of Greek poetry. That word was 'hormone', based on the ancient Greek word for 'I arouse', or 'I excite', and the term stuck.

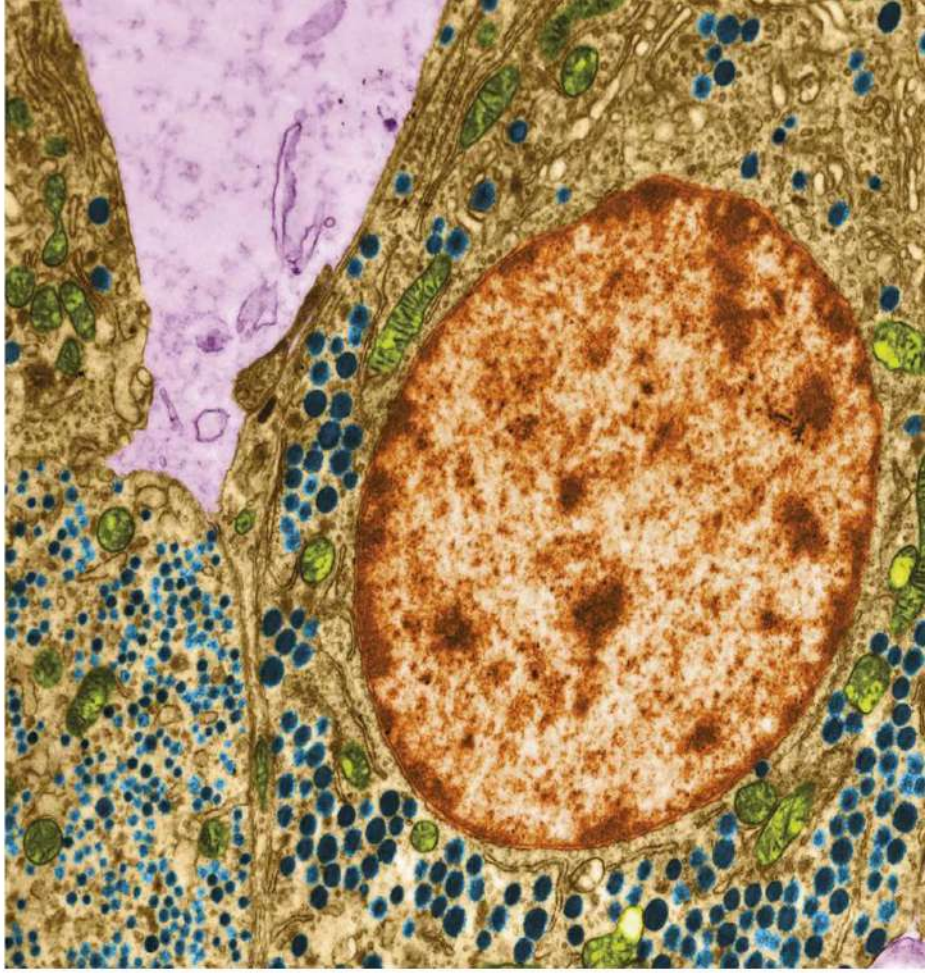
From here, advancement in endocrinology began to gather pace. In 1921 Frederick Banting and Charles Best discovered insulin, the hormone that tells the body to absorb sugar from the bloodstream. The pair's elegant experiment would lead to a treatment that still saves millions of lives.

Before Banting and Best's discovery, those with diabetes often succumbed to a slow and painful death at a young age. Type 1 diabetics do not produce enough insulin, meaning the sugar from the food they consume remains in their blood instead of being absorbed into their tissues for energy.

Banting and Best started by removing the pancreas of a dog. The dog quickly became diabetic, indicating that the pancreas had a key role in the disease.

The majority of tissue in the pancreas secretes digestive juices, but the pair believed the organ had another function. In another dog, they tied up the pancreatic duct with string, causing the digestive juice-producing cells of the pancreas to wither and die. Ingeniously, what it left them with was just the cells of the pancreas they wanted to experiment on; these are now known as pancreatic islets. After extracting the secretions from just these cells, they injected them into the diabetic dogs. Their blood sugar levels quickly returned to normal levels.

A year later, after working out how to purify their mixture, they injected their first human patient. Soon, they were personally injecting



Seen through the gaze of a transmission electron micrograph, a colour-enchanced cell (orange) in the pituitary gland can be seen secreting hormones (light green)

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TIMELINE

Once scientists had established the significance of glands, it didn't take long to get to grips with hormones

1700s

The height of the craze for 'castratos' – male opera singers castrated before puberty. Giuseppe Aprile was one of the most famous.

1849

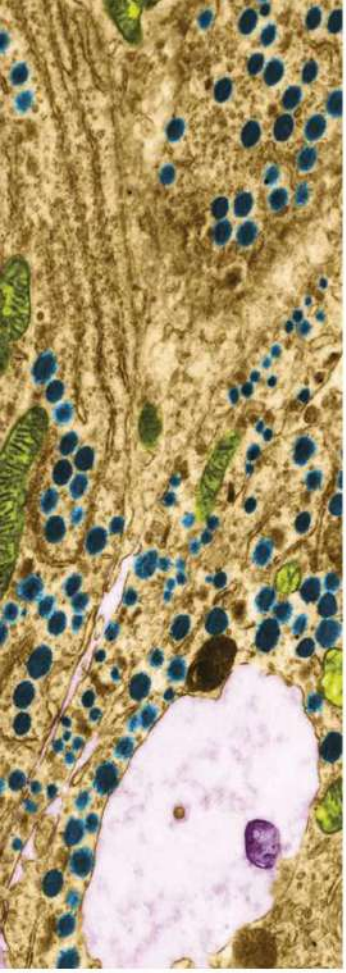
Arnold Berthold's famous experiment on cockerels reveals that the testes play a key role in the development of male characteristics, even when severed from the nervous system.

1891

George Redmayne Murray cures myxedema patients using extracts from the thyroid glands of sheep.

1905

Ernest Starling uses the term 'hormone' to describe the chemical messengers that are rapidly being discovered.



AFTER WORKING OUT HOW TO PURIFY THE MIXTURE, THEY INJECTED THEIR FIRST HUMAN PATIENT

entire wards of diabetic children, who quickly roused from their deathly stupor. Within two years of Banting and Best's discovery, the pharmaceutical company Eli Lilly was making enough insulin, produced from animals such as oxen, to treat all the diabetics in North America. By the 1960s, the hormone was being created synthetically without the need for animals.

NEW DISCOVERIES

Modern endocrinology was now in full swing, and there were many breakthroughs throughout the rest of the century. Many of them came thanks to the ability to measure minute quantities of hormones circulating in the blood. Such precise measurements would be impossible without a technique called 'radioimmunoassay', developed by an American physicist Rosalyn Yalow.

Yalow was awarded the Nobel Prize in 1977 alongside the endocrinologists Roger Guillemin and Andrew Schally. Her technique allowed Guillemin and Schally to measure the tiny concentrations of pituitary hormones in the blood. The work was vital in understanding the pituitary gland's role as a regulator of other hormone glands. Sometimes known as 'the master gland', the pituitary links the brain's hypothalamus region with the rest of the endocrine system. It is a crucial connection between the outside world, your senses and your body's chemical response system.

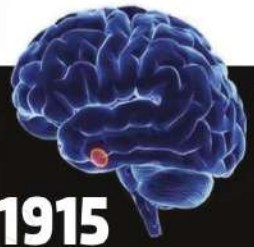
According to endocrinologist Dr Saffron Whitehead, Yalow's radioimmunoassay and the development of high-resolution imaging are what have driven almost all of the advances in modern endocrinology over the last 50 years. "The ability to do immunoassays has revolutionised endocrine research and diagnostics. For the first time levels of circulating hormones could be accurately measured," she says.

Today, our understanding of hormones has grown immensely – scientists have discovered around 80 human hormones so far, and we now know that more tissues than just the endocrine glands produce them. Work is ongoing to unravel the complex relationships between hormones and obesity, cardiovascular disease, depression and ageing. Understanding the link between genetics and the hormonal system will also keep endocrinologists busy for years to come.

Dr Whitehead believes there are still many hormones to be discovered. "I think we will find that as well as being secreted into the bloodstream, there are hormones that act locally, between cells."

Today, endocrinology is at the cutting edge of the life sciences – using modern lab techniques and computer modelling to understand the immensely complex biochemical systems that keep us alive. But modern science owes much to the physicians from the Victorian era, who first conducted those early and grisly experiments. **SF**

by **TOM IRELAND** *(@Tom_J_Ireland)*
is editor of ***The Biologist****, the Society of Biology's magazine.*



1915
Harvey Cushing starts his work on the pituitary gland – the 'master gland' that keeps many other metabolic processes synchronised.

1921
Insulin therapy for diabetics is developed by Frederick Banting and Charles Best. Banting is awarded a Nobel Prize two years later – he shares his money with Best.

1977
Roger Guillemin and Andrew Schally, Rosalyn Yalow share a Nobel Prize. Yalow's 'radioimmunoassay' allowed Guillemin and Schally to measure tiny amounts of pituitary hormones in the blood.

BREAKTHROUGHS

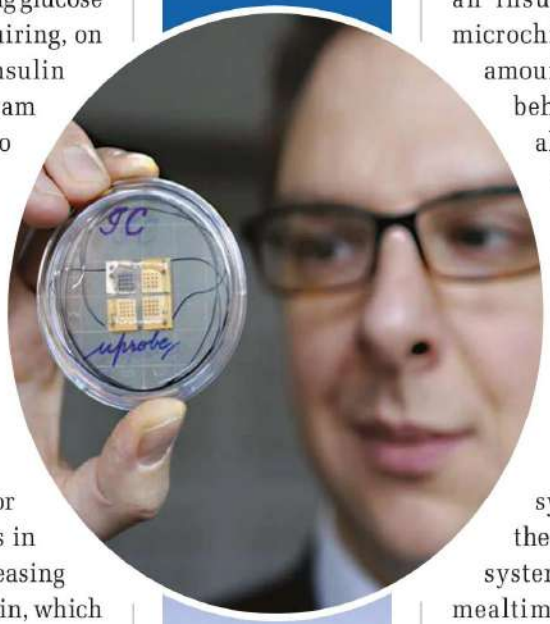
Computer-controlled diabetes

Managing diabetes means an ever-changing daily regime of multiple, self-administered insulin injections. But what if there was a device that could do the managing for you?

words by SARA RIGBY

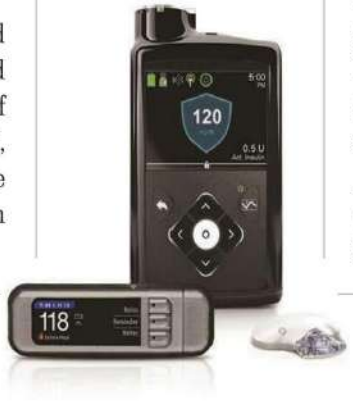
For someone living with type 1 diabetes, monitoring and maintaining glucose levels can be a chore, requiring, on average, an injection of insulin between two and six times a day. A team at Imperial College London is aiming to make their lives easier by developing a device dubbed the 'bionic pancreas'. "It will be a revolution both in terms of glucose control and quality of life for people living with diabetes," says Dr Pau Herrero-Vinas, an engineer on the team.

The pancreas is a small, pear-shaped organ that controls blood sugar levels. The cells responsible for this job, beta cells, respond to spikes in glucose levels by simultaneously releasing and manufacturing the hormone insulin, which allows glucose to be absorbed into tissue. When not enough insulin is produced, glucose builds up in the bloodstream and, past a certain point, can lead to coma and death. High blood sugar levels, also known as hyperglycaemia, can cause blindness, heart disease and nerve damage over the long-term.



ABOVE: Dr Nick Oliver, part of the team developing the Bio-inspired Artificial Pancreas, with a prototype of the device

BELOW: The MiniMed 670G 'hybrid 'system is already available but requires the user to input info about the food they're consuming



TECHNOLOGY STEPS IN

In people with type 1 diabetes, the pancreas contains only 20 to 30 per cent of the regular number of beta cells, meaning that insulin levels are dangerously low unless treated with regular injections of insulin.

The bionic pancreas, or the Bio-inspired Artificial Pancreas for the Home, is designed to act like a replacement organ. The process of regulating blood sugar levels is fully automated, so the device is constantly monitoring glucose levels and making small changes to keep them under precise control.

The device is comprised of a glucose sensor, an insulin pump and a microchip. The microchip's algorithm calculates the precise amount of insulin needed, mimicking the behaviour of beta cells. By embedding all the software onto a microchip, the team created a device that not only requires small amounts of power, but is also compatible with other medical devices the user might need. "We focussed on developing a system that is very low-power so that it can be embedded in any medical device," Dr Herrero-Vinas explains.

There is another artificial pancreas system, the MiniMed 670G, already on the market, but it is known as a 'hybrid' system since it isn't fully automated. At mealtimes, the user still needs to give the device information about the carbohydrates they're about to eat so that it can calculate the correct insulin dose. When the user isn't eating, though, the MiniMed works happily on its own – meaning it is most effective overnight. "Overnight control is a problem that's already been solved, so it's not very challenging anymore," says Dr Herrero-Vinas. "But daytime control, especially after meals, that's still a problem. So that's what we're focussing on: to have a system that works at night and through the day."

The bionic pancreas is currently being clinically tested. Once these tests are complete, says Dr Herrero-Vinas, the team will look at licensing the product to make it available to patients, which he estimates will happen in a couple of years. **SF**

by SARA RIGBY

Sara is BBC Science Focus Magazine's online assistant.

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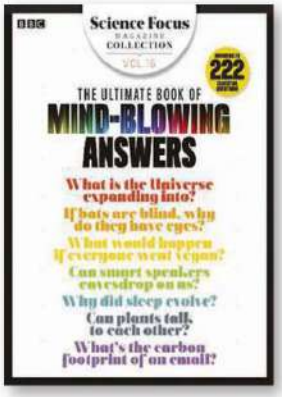

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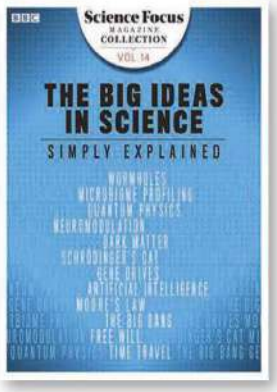

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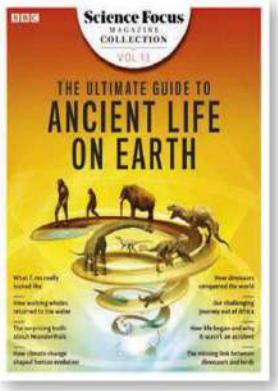

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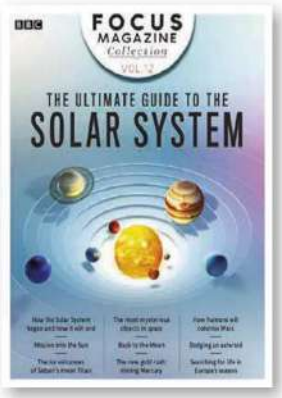

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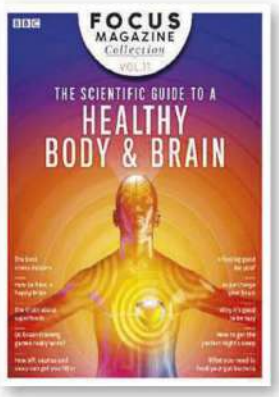

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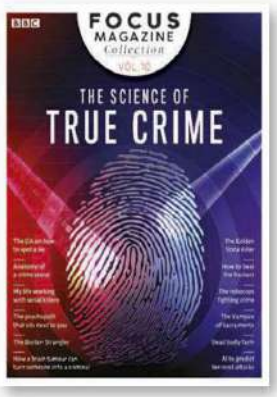

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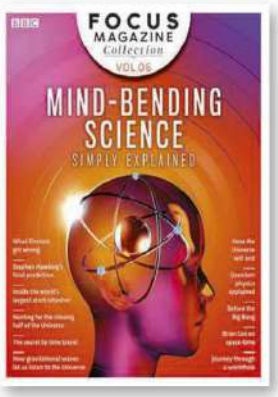

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Integumentary SYSTEM

Your skin – a membrane that in certain places is less than a millimetre thick – is all that stands between your internal organs and the outside world. But this thin, flexible covering is able to protect you and your insides from an astounding array of physical, chemical and biological threats. And if something does manage to damage it, it's capable of repairing itself. Meet your skin... your body's biggest and most overlooked organ

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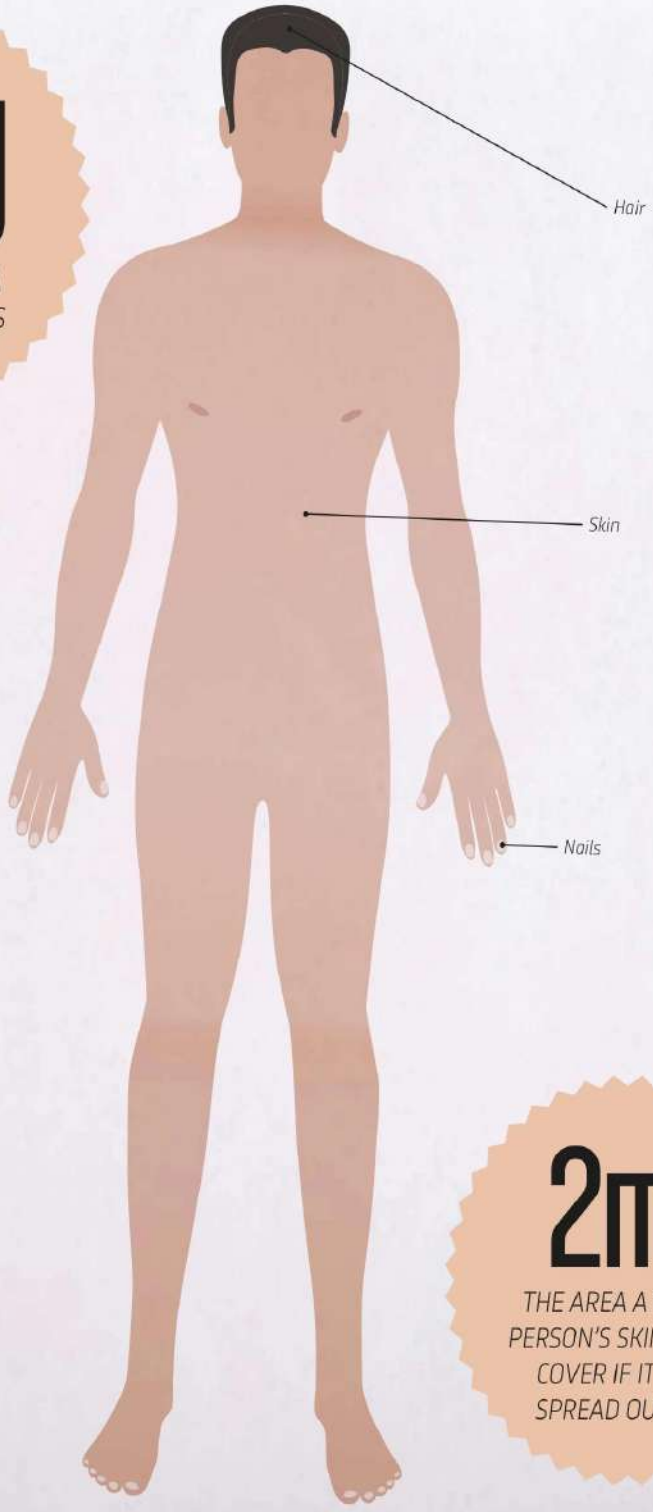
9kg

THE WEIGHT OF A TYPICAL PERSON'S SKIN



$2m^2$

THE AREA A TYPICAL PERSON'S SKIN WOULD COVER IF IT WERE SPREAD OUT FLAT

EVERYDAY ARMOUR

It's waterproof, changes colour in the Sun, helps you keep cool in the heat and grows harder to cope with friction. Your skin is an multi-layered membrane that spends every moment multitasking and gets nothing like the recognition it deserves

words by DR MONTY LYMAN

GETTY IMAGES

What is our most human organ? If you asked most people which characteristic has, more than any other, enabled our species to not only survive and thrive, but ultimately dominate the planet, they'll probably say 'brain sophistication' or 'thumb dexterity'. But the human story could never have happened without our skin. Skin is an astoundingly diverse organ and its significance to the advancement of humans can be seen in just three of its seemingly unromantic qualities: its sweatiness, its nakedness and its toughness.

DON'T SWEAT THE SMALL STUFF

No matter what the outside temperature is, your body needs to tread an inner tightrope between 36°C and 38°C, and anything much above 42°C is lethal. The highly intelligent, but heat sensitive, human brain could never have spread across the globe without a body capable of carrying it long distances in hot climates. What made it possible is the human body's industrious eccrine sweat glands. These glands are shaped like strings of spaghetti, with one end coiled up in the deepest of the two layers of the skin – the dermis – and the rest of the tube stretching all the way to the surface, passing the upper 'epidermis' and opening up in a sweat pore.

Your skin carries four million of these glands, and together they are capable of pumping

out literally bucketloads of sweat each day, with some people capable of sweating three litres an hour. On a hot day, the brain's sensitive hypothalamus detects a rise in your body's core temperature and fires signals along autonomic (unconsciously acting) nerves to the eccrine glands, instructing them to send sweat to the surface of your skin. When sweat – essentially water with a few trace particles of salts – lies exposed on naked skin, it rapidly evaporates. The process of evaporation removes high-energy, heat-containing molecules from your body, immediately cooling your skin and the blood vessels of the dermis. The cooled venous blood then returns from your skin to the core of your body, preventing a dangerous rise in your core temperature.

You have eccrine sweat glands all over your skin, but their density is greatest on the palms of your hands and soles of your feet. But these areas do not seem to produce a larger volume of sweat in response to heat and exercise; instead, the glands on your hands and feet respond keenly to another stimulant of autonomic nerves: stress. This explains why you get clammy hands before an interview, no matter what the temperature. Perhaps surprisingly, the sweat on your palms and soles actually increases friction and grip on the skin's surface, as your body readies itself for grappling with an enemy or fleeing up a tree.

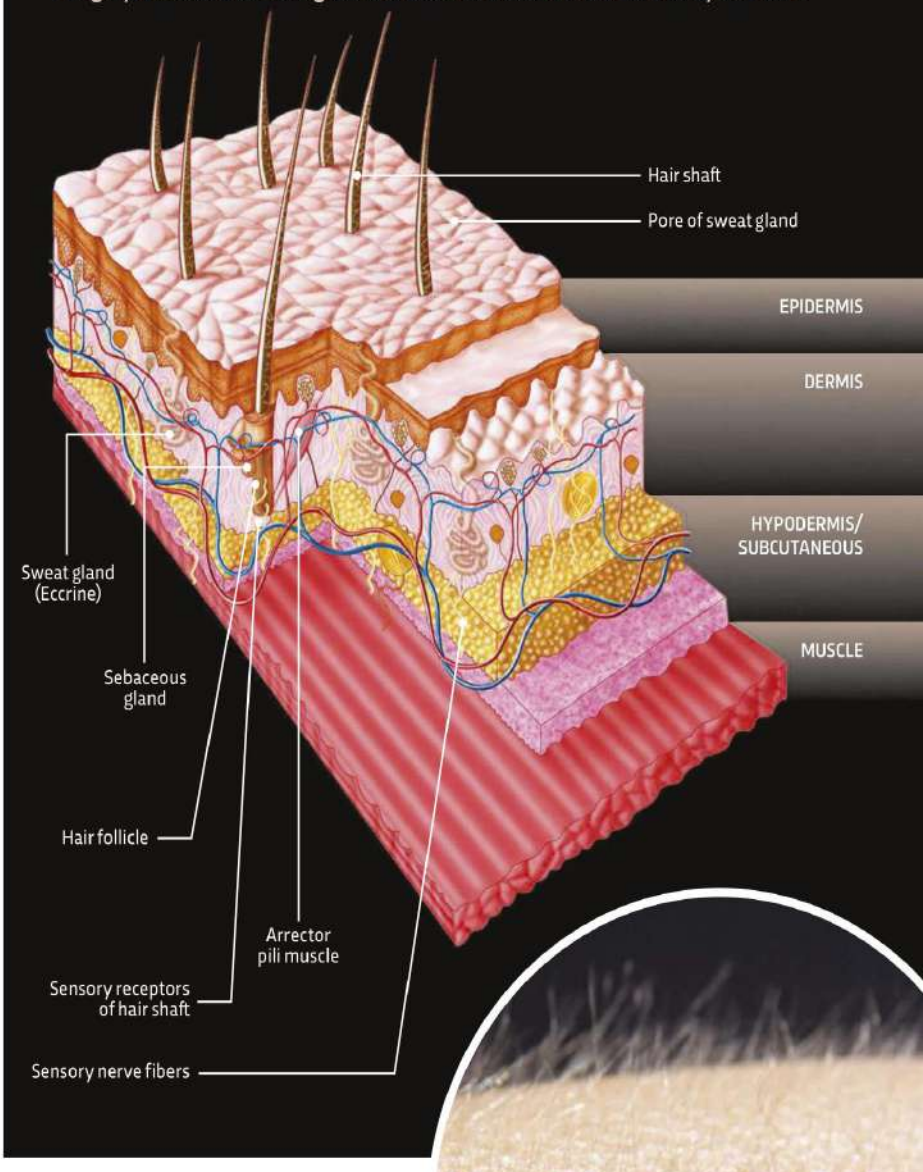
Sweat cools you down and is defensive, but could it also help you find a partner? Another type of sweat factory in your dermis is the apocrine gland. These are physically similar to eccrine glands but their product, which is oily, has served a very different purpose in the propagation of humankind; apocrine glands are found in the armpits, the nipples and the groin, hinting at their likely roles in lovemaking.

Apocrine sweat is itself odourless but its smorgasbord of proteins, steroids and lipids is a feast to the legion of bacteria on your skin, which metabolise it into the not-so-sweet smell of body odour. It has long been thought that this natural eau de parfum contains pheromones, chemical compounds that trigger a physical or social response in other people.

Although science still hasn't pinned down the exact molecules that may influence perceived attractiveness, humans are nevertheless exquisitely proficient at detecting their partner's 'odour print'. A prolonged sniff of your loved one will trigger happy memories and reduce stress levels. One study even found that, when sniffing sweaty t-shirts, women are more attracted to the sweat of men with dissimilar immune genes. Our skin-nose communication may be helping us avoid incest and diversify our offspring's immune systems.

LAYERS OF SKIN

Your body's biggest organ is constructed from three layers that combine to form a highly effective barrier against the outside world. Here's what in your skin...



THE NAKED TRUTH

The nakedness of our skin is another key feature to the success of the migrating human.

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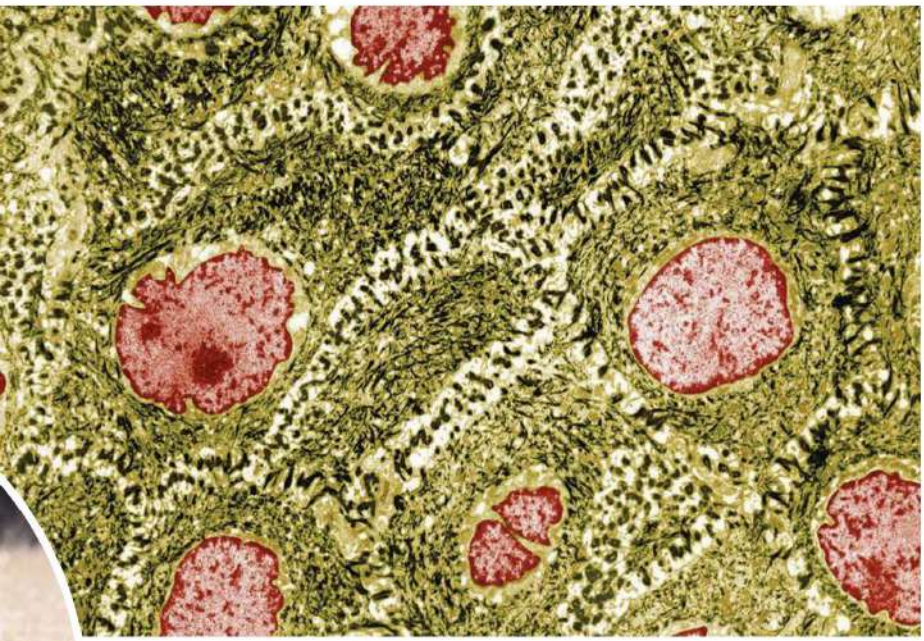


TOP: Sweating prevents your body from overheating when the temperature rises

ABOVE: Multiple layers of keratinocyte cells form the epidermis, the outer layer of your skin

LEFT: Tiny muscles attached to each hair follicle pull the hairs upright to trap a layer of warm air next to your skin

Compared to most mammals, human body hair is conspicuous by its absence, and our lack of it is critical for evaporation when we need to lose heat. Conversely, when we need to stay warm, although we don't have a thick layer of fur, our hair follicles – found among sweat glands in the dermis layer of the skin – work together to form a temporary covering.

The hair shafts on our skin usually lie flat, but when it's cold the tiny arrector pili muscle attached to each hair follicle in the dermis contracts. This contraction makes the hairs stand up, trapping a thin layer of warmer air above the skin and creating a temporary coat. The skin's thermostat walks a fine line, then, continuously checking and responding to our temperature in order to keep us alive.

COMPARED TO MOST MAMMALS, HUMAN BODY HAIR IS CONSPICUOUS BY ITS ABSENCE

TOUGH AS OLD BOOTS

Above the hustle and bustle of the dermis, perched on the very edge of your body, lies the epidermis (literally, 'on the dermis'). It is on average less than 1mm thick, little more than a sheet of paper, yet it carries out almost all the barrier functions of your skin and survives all manner of damaging encounters, which it is exposed to far more often than other body tissue.

Its secret lies in its multi-layered living brickwork formed of keratinocyte cells. The epidermis is made up of between 50 and 100 layers of keratinocytes, named after their structural protein, keratin.

Keratin is unbelievably strong: it forms our hair and nails, as well as the claws and horns found in the animal kingdom. The word itself comes from the Ancient Greek for horn: keras (from which we also get rhinoceros).

If you were able to zoom in on the back of your hand to about 200x magnification, you would see tough, interlocking keratin scales resembling an armadillo's armour. This biological chainmail is the culmination of the remarkable life of the keratinocyte. Keratinocytes are ➲

constantly being formed from stem cells in the deepest layer of the epidermis and slowly move up in layers throughout their month-long lives until they form a formidable barrier, as waterproof as a raincoat, before flaking off into the atmosphere.

When your outer layer is repeatedly beaten and battered, your epidermis responds by going into overdrive, and any areas of your epidermis that encounters frequent friction is likely to develop calluses, such as those found on the palms and fingers of builders and rowers.

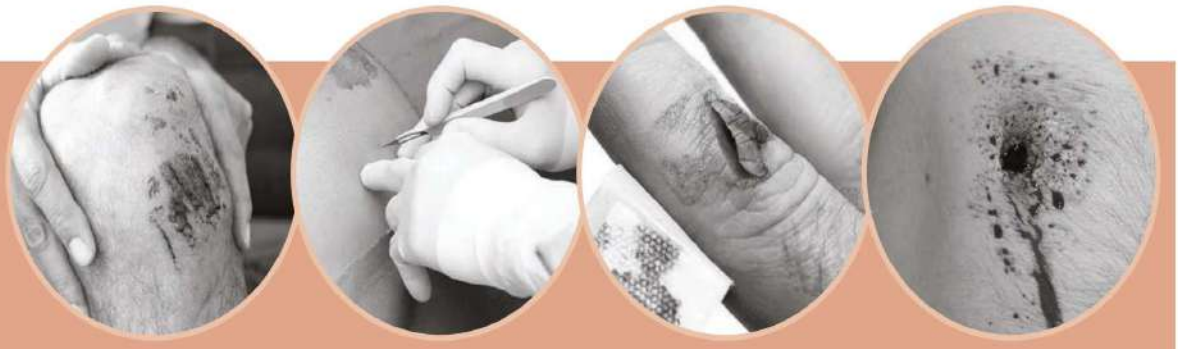
Even when your skin barrier is breached, it has remarkable healing properties. If your skin is cut, it springs into action and begins to compose a four-movement symphony.

The skin's first priority is to stop the bleeding, which it does within minutes through pain receptors causing blood vessels to contract and platelets – disc-shaped cells in the blood – to stick to proteins in the now-exposed dermis and bundle together to form a sticky plug. Then, over the next few days, the immune cells of the skin are given two roles: the military imperative of killing bacteria that enter your body through this breach in your skin's defences; and the disaster-relief, clear-up task of removing debris and destroying dead cells. After that your skin's builders, the fibroblasts, get to work. These start to rebuild the wreckage by producing new collagen and proteins that aid the healing process. Finally, keratinocytes now slowly crawl from the wound edges across this bed of new tissue, with the new tissue aligning with the normal tension lines of your skin.

Skin is our largest and most visible organ but, despite us seeing and touching it – indeed living in it – every moment of our lives, it is the organ most overlooked by the medical profession. Weighing nine kilograms and covering two square metres, skin wasn't even recognised as an organ until the 18th century. Human skin's sweatiness, nakedness and toughness show that it's not just a marvellous material, but an intricate organ that's vital for our survival and success. **SF**

by **DR MONTY LYMAN** *is a junior doctor and the former national head of undergraduate and junior doctor dermatology in the UK. His book* ***The Remarkable Life of The Skin*** *is out now.*

SKIN DAMAGE



You can harm your skin in all sorts of ways but physically inflicted wounds break down into four types...

1 ABRASION
Commonly known as a graze, this is caused by shearing forces that scrape off the epidermis, the outer layer of skin. Abrasions will be familiar to anyone who has fallen off a bike and slid along a hard road. As these do not usually affect the dermis, no scar tissue is formed.

2 INCISION
A neat wound caused by a sharp object, such as a scalpel or the edge of sheet of paper. Even without stitches, your skin can knit the edges of the wound together. During the healing process, some of your skin's builder cells, the fibroblasts, can transform into muscular 'myofibroblasts', which pull the wound together at a rate of 1mm a day.

3 LACERATION
Similar to incisions, these wounds cut down into the dermis and below, but have rough, jagged edges. These are caused by the tearing forces of blunt trauma. Minor lacerations can be treated by stopping the bleeding, cleaning the wound with warm water, soap and an antibiotic ointment and applying a sterile bandage.

4 PUNCTURE/ PENETRATION
A wound caused by an object piercing the skin, ranging from a splinter to a bullet. Due to kinetic forces, the amount of damage is more related to the speed of the object than its size.

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BREAKTHROUGHS

Fixing broken skin

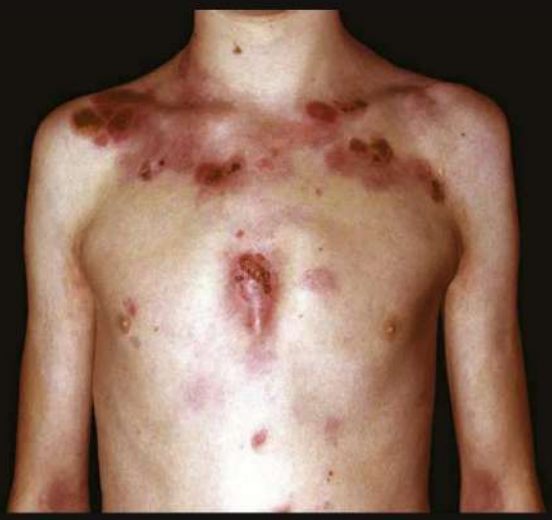
New medical techniques can help mend our outer membranes

Skin is at the forefront of many revolutions in modern medicine. New medications containing antibodies that target specific molecules – known as monoclonal antibodies – are incredibly effective at treating autoimmune and inflammatory diseases. These have transformed the treatment of moderate to severe psoriasis, which soon may be a thing of the past, and new monoclonal antibodies for eczema are looking very promising. Recent leaps in the understanding of our skin's microbiome are also opening up new avenues of treatment, such as the research that suggests underarm bacterial transplants could be the cure for body odour.

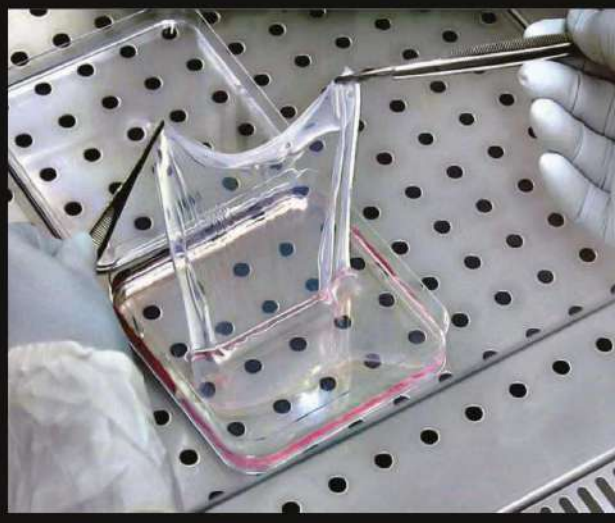
Remarkably, one recent case involving a seven-year-old Syrian immigrant called Hassan, living in Germany, shows the skin as the laboratory for two emerging fields poised to revolutionise medicine: stem cell therapy and gene therapy.

Hassan was born with a genetic condition called epidermolysis bullosa, caused by a mutation in the LAMB3 gene, in which the proteins that tightly anchor the epidermis to the dermis are missing. A shearing force as light as twisting a door handle would rip off the epidermis of his hand, causing immense pain and breaking the all-important barrier, letting water out and microbes in.

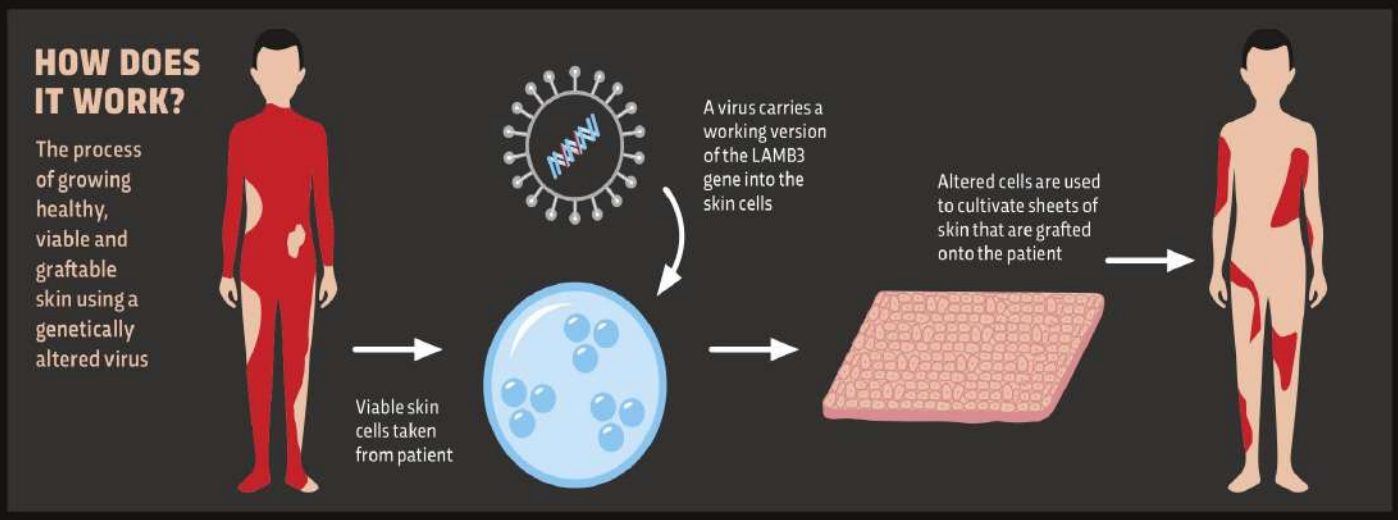
The only viable skin left on Hassan's body clung to his face, left thigh and a few patches on his trunk. In this state, he didn't have long to live. Almost half of the children with this condition never make it to adolescence. But in 2015 a team from University of Modena and Reggio Emilia, Italy, took some of his skin cells, infected them with a virus that contained a healthy version of the LAMB3 gene, and grew nine square feet of this renewed skin in the lab. They replaced his skin in two operations and, amazingly, when the study was published, two years after this experimental operation, Hassan's skin was still completely intact. The stem cells incorporated in the new skin were producing fresh, healthy skin cells for perpetuity.



ABOVE: Epidermolysis bullosa prevents collagen from forming between skin layers, allowing them to move freely across each other and create painful sores



BELOW: Sheets of genetically modified skin cells can be cultivated to match a patient and bypass the problem of their body rejecting the graft



Immune SYSTEM

When your body comes under attack, it's your immune system that fights off the invaders. The fact you have an army stationed inside your body that's on high alert around the clock, always ready to spring into action, is amazing in its own right. But what's more extraordinary is how that army identifies enemies and the methods it uses to defeat them

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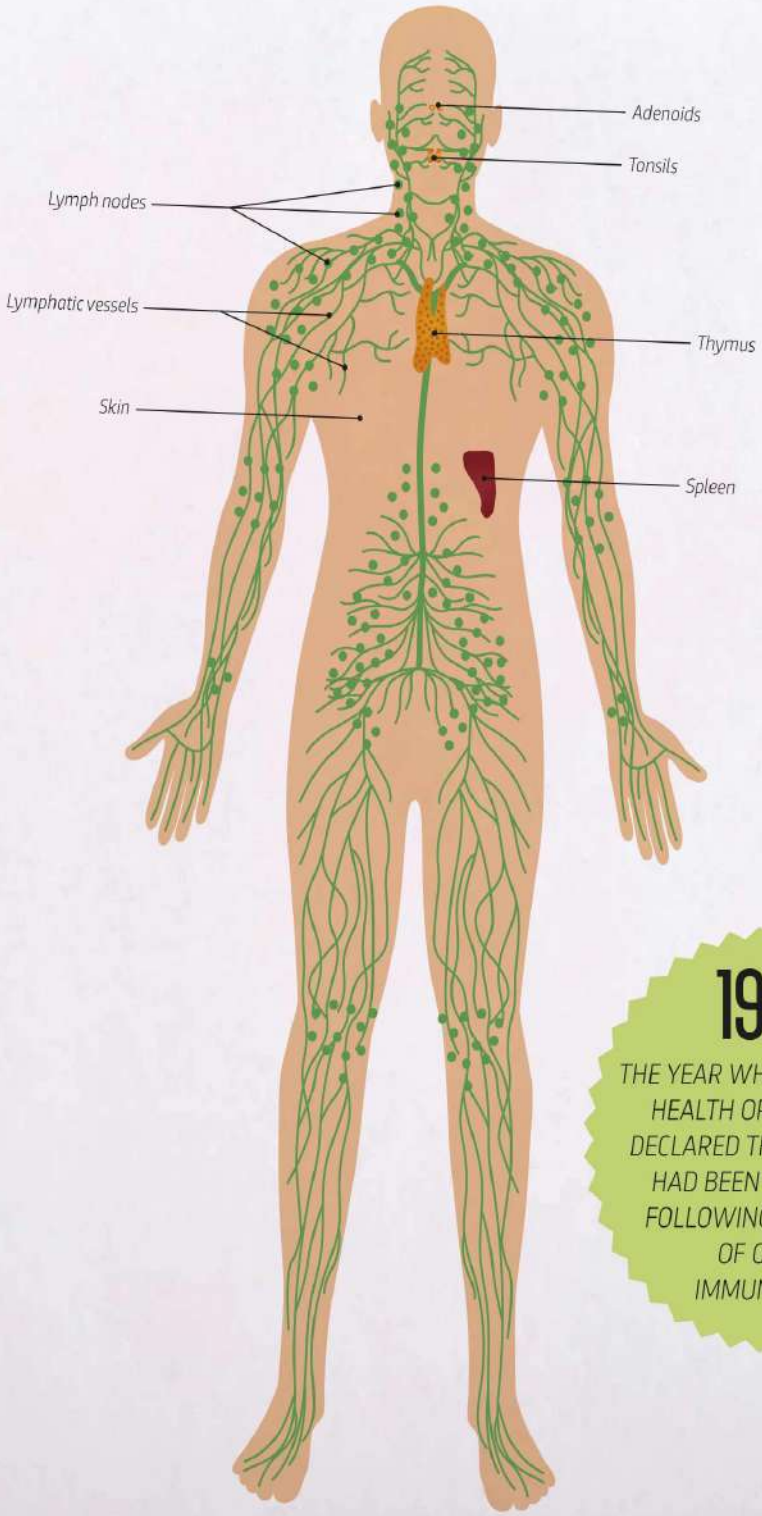


1980

THE YEAR WHEN THE WORLD HEALTH ORGANISATION DECLARED THAT SMALLPOX HAD BEEN ERADICATED, FOLLOWING A PROGRAM OF GLOBAL IMMUNISATION

There's a reason you feel so unwell when you're fighting off an infection… an army of organisms and substances has been deployed to defend your body against the attack

words by SALEYHA AHSAN

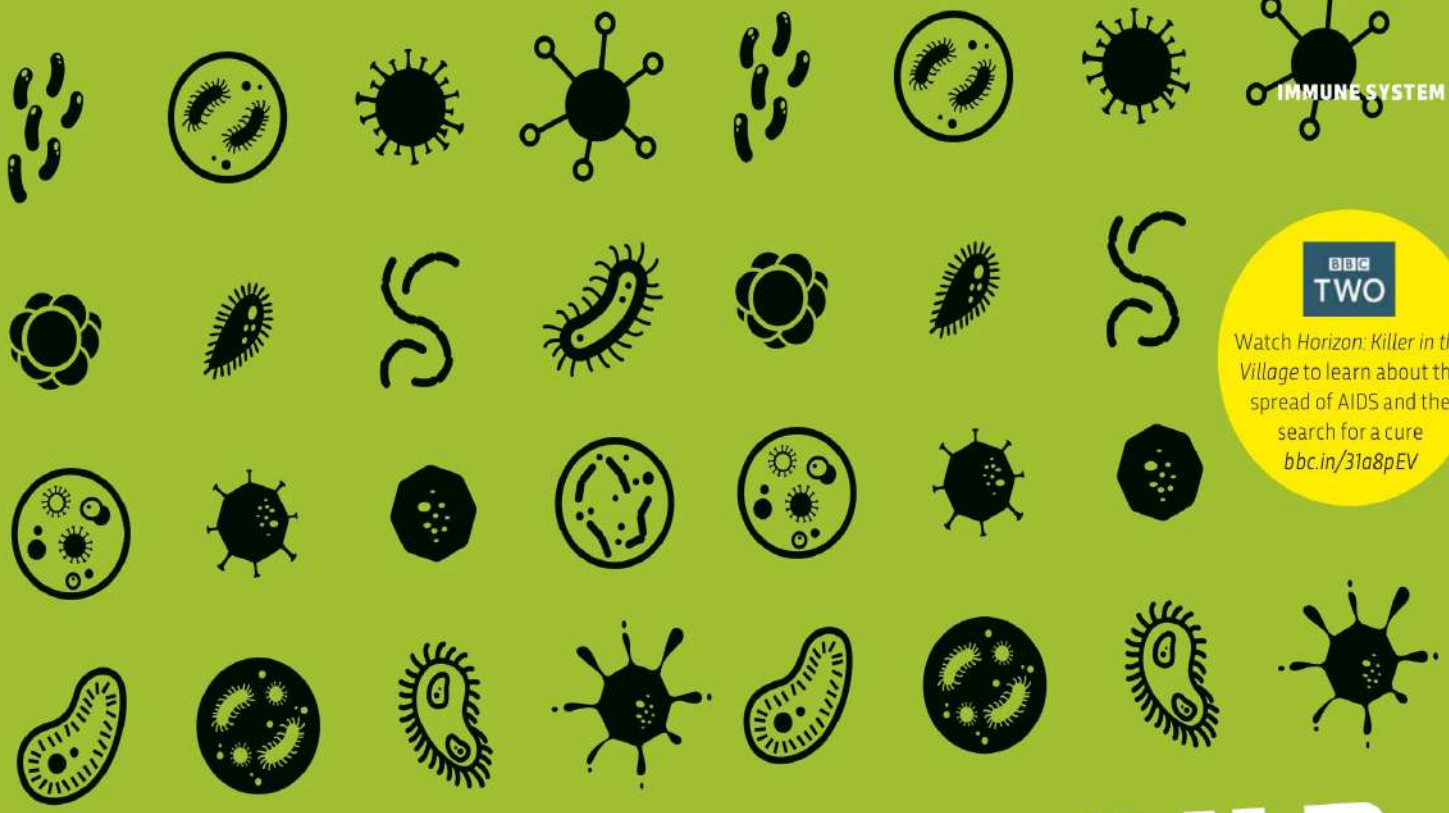
YOUR BODY THE

Your immune system is the feistiest part of your body. It needs to be – your body is constantly under attack from millions of pathogens that are trying to get inside and do you harm and it's your immune system's job to fight them off.

Every part of your body has a role to play in repelling these attacks, from your skin (your body's biggest organ) to the microscopic bacteria that live in your gut. But it's not a static system. Your immune system learns and evolves in order to provide you with protection against any new pathogens you encounter. But it also has a memory. If a particular pathogen is experienced twice, your immune system recognises it the second time, and because it knows the enemy, it can fight it off faster.

The first line of defence is your skin, which acts as a waterproof barrier to outside pathogens. That's why medical staff worry about the risk of infection when someone suffers extensive burns – their body's physical barrier is compromised.

Specific points of attack have their own equivalents of sentries standing guard. Cavities, such as your nose and mouth, are lined with membranes that produce sticky mucus to trap bacteria and other pathogens. If intruders arrive in your nose, reinforcements are sent in to get rid of them, which is to say you'll be producing more mucus. Saliva in your mouth washes pathogens from your teeth, helping to reduce the amount of bacteria in there. Should any invading forces breach these defences, your stomach also creates an environment hostile to threatening bacteria. Acidic gastric juice helps kill most bacteria in food or anything else that makes it into your digestive system.



BBC TWO

Watch *Horizon: Killer in the Village* to learn about the spread of AIDS and the search for a cure *bbc.in/31a8pEV*

BATTLEGROUND

When your immune system detects an intruder, it sounds the alarm to rally the troops and mount a defence. But instead of the sound of sirens, you get a fever (a body temperature above 37.5°C), which stimulates your immune system to help it fight off the infection by making it harder for pathogens to survive.

IDENTIFYING THE THREAT

Despite all the barriers your body puts up, some pathogens manage to break through and once inside, they breed and cause you to feel unwell. This is when your immune system steps in to fight it, but before it can attack an intruder it has to identify it. And it does that by reading antigens – protein 'fingerprints' on cell surfaces – in order to determine whether the cells it encounters are yours or those of an invader.

The foot soldiers at this level are an army of white blood cells. Their mission is to destroy invading pathogens. There are different types with different roles, just like real military regiments, but they all have the same purpose: to fight infection.

You have lymphocytes (T cells and B cells) that attack viruses, neutrophils that respond to bacterial attack and then there are the monocytes, macrophages, eosinophils and basophils. They're stationed in locations all around your body, including your thymus (in your trachea, between your collar bones), spleen, tonsils, blood vessels, lymph nodes (primarily in your neck, armpits and groin), small intestine and adenoids (in your nose).

The B and T cells are created by the stem cells produced by the marrow in your bones. B cells remain in your bone marrow while the T cells migrate to the thymus, where they mature. In the thymus T cells are taught to discriminate between your body's own cells and those of pathogens, and then kill any they ➤

GETTY IMAGES X2

detect. When this learning process fails, people develop autoimmune diseases, where the body attacks itself (see 'Friendly fire', opposite).

T cells directly attack invading organisms but need help recognising their antigens from those of other cells. When they encounter an antigen only a few T cells are able to recognise and bind to it initially. They don't attack straight away; they keep it under close surveillance while they wait for confirmation of its identity. If the antigens are identified as invaders, the signal to attack is given and the T cells are activated – they begin to grow and divide, targeting any cells they find with the same antigens and releasing chemicals that destroy them.

B cells, on the other hand, can recognise the antigens of invaders on their own and take action immediately. When they come across one, they produce antibodies to destroy it. Antibodies can immobilise bacteria, encourage other cells to 'eat' the pathogen and activate other immune defences. Not all B and T cells are expended in the process of identifying and destroying antigens. Some live on as memory cells that respond more vigorously should the same antigen show up again.

CONTAIN THE CONFLICT

The third part of your immune system is the lymphatic system. It's a network of vessels carrying lymph fluid, which contains white blood cells – your infection fighting forces.

Lymph nodes are found in lymph vessels and they filter the lymph fluid flowing through the vessels. The nodes contain lymphocytes (B and T cells), which recognise bacteria and pathogens that have entered the lymph fluid via the bloodstream and destroy them.

When foreign material is detected, other dedicated immune cells are recruited to the node to deal with the infection. This helps to prevent the infection from spreading throughout your body, like gates shutting off routes for invading bacteria.

Lymphoid tissue also helps to defend mucosal surfaces from infection. Your tonsils become enlarged in response to infection as they trap pathogens, activating white blood cells.

Experience improves your immune system's performance. The first time your body comes into contact with a particular pathogen, your immune response may take a while to deal with it. It could be a few days of feeling rough as the pathogen-fighting forces battle to get rid of the infection. But if you come across that same pathogen again, your body remembers it and fight it off faster. This principle led to the development of vaccines, which are designed to help your B and T cells learn how to fight off pathogens and provide long-term immunity by exposing them to a manageable sample of the pathogen.

B and T cells need time from the initial pathogen exposure to become activated. This activation lag time is when you feel the infection at its worst. If it's flu, for example, it makes you lethargic, achy, fatigued and unable to get out of bed. Vaccines help to speed up the response time by introducing fragments of the infection into your body. This exposes you to the pathogen without you having to suffer the actual infection. Your immune system then becomes trained and the army of B and T cells can mobilise quicker when the pathogen strikes for real.

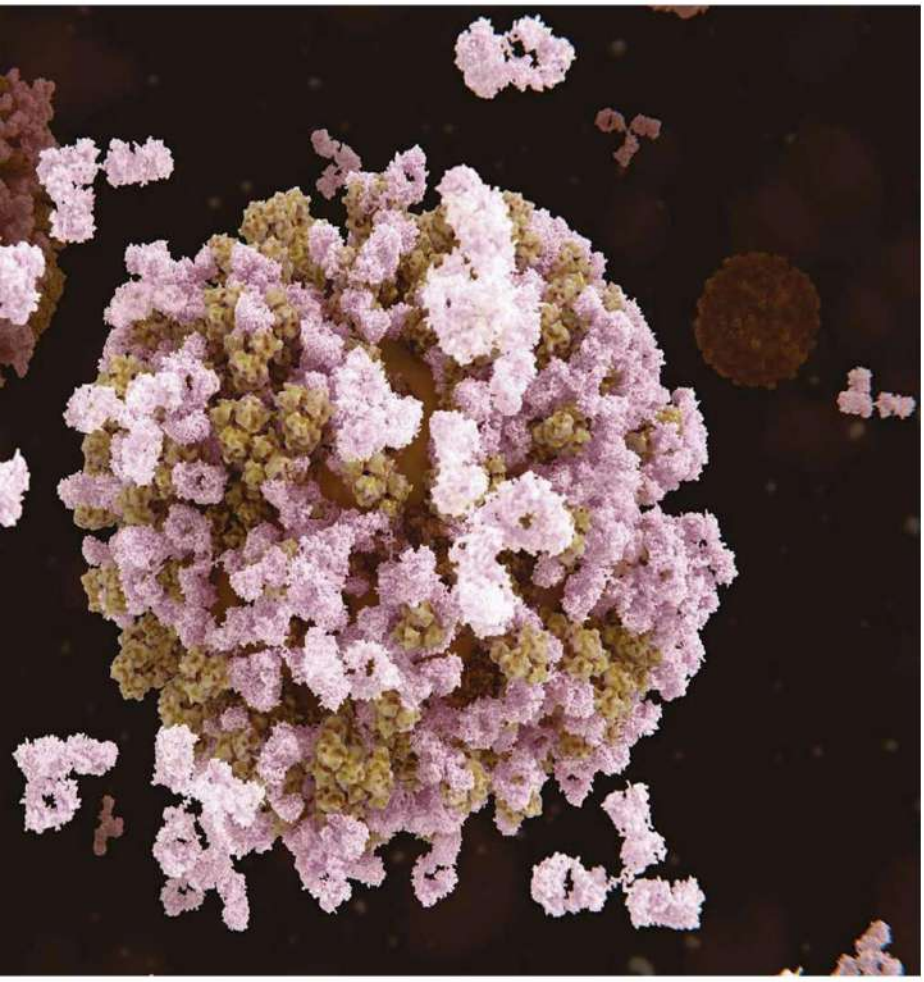
Once a certain threshold has been reached, herd immunity gradually eliminates a disease

To do all this, the infection-fighting cells need quite a bit energy, so if you're stressed, sleep deprived, not eating properly or over doing it, their batteries will be running low. This is when you're most susceptible to infection.

Immune suppression means your immune system isn't working properly, leaving you more vulnerable to infection. You're likely to need to see a doctor, require antibiotics and possibly even hospital care to help you overcome infection compared to someone who is not immunosuppressed. You also cannot have live vaccines and may need to take special precautions when you travel.

There are various causes of immunosuppression, including age and chronic diseases such as diabetes mellitus, but also certain medications, particularly those to stop your body rejecting transplanted organs, and certain cancers such as lymphomas, leukaemia and myeloma.

It is for this group of the population, that herd immunity is most important. Herd immunity



Antibodies (pink) bind to and attack flu virus particles (brown) in the process of fighting off the infection

occurs when a large percentage of a population has become immune to a contagious infection, which in turn provides a measure of protection for those who are not immune because it becomes harder for the disease to spread. The greater the proportion of a community that is immune, the smaller the probability that those who aren't will come into contact with an infectious individual.

Individual immunity, whether gained through recovering from the infection or vaccination, helps those who are unable to develop their own. Once a certain threshold has been reached, herd immunity gradually eliminates a disease from a population. If it reaches global level then we have the ultimate situation: eradication, as happened with smallpox in 1980.

Mass vaccination to induce herd immunity has since become common and proved successful in preventing the spread of many infectious diseases. Opposition to vaccination has posed a challenge to herd immunity, allowing preventable diseases such as measles and polio to persist in or return to communities that have inadequate vaccination rates thus putting those with compromised immunity at greater risk. Herd immunity is nature's way of testing society's humanity for those who need our help. **SF**

by **SALEYHA AHSAN** (@SaleyhaAhsan)
Saleyha is a practising A&E doctor and a presenter on BBC Two's Trust Me I'm a Doctor.

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FRIENDLY FIRE

What happens when your immune system goes on the attack but there's no enemy on the battlefield?

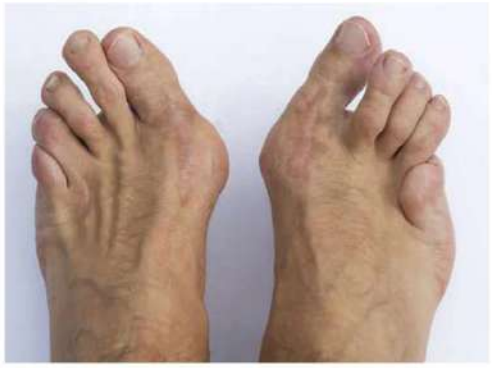
Autoimmune disorders occur when the body produces an immune response against itself. There are more than 80 known types of autoimmune disorders.

The cause of autoimmune diseases is unknown, but there may be a genetic link in many cases. In a few types of autoimmune disease, a pathogen triggers the immune system as normal, but the antibodies or T-cells produced attack normal cells, as in rheumatic fever.

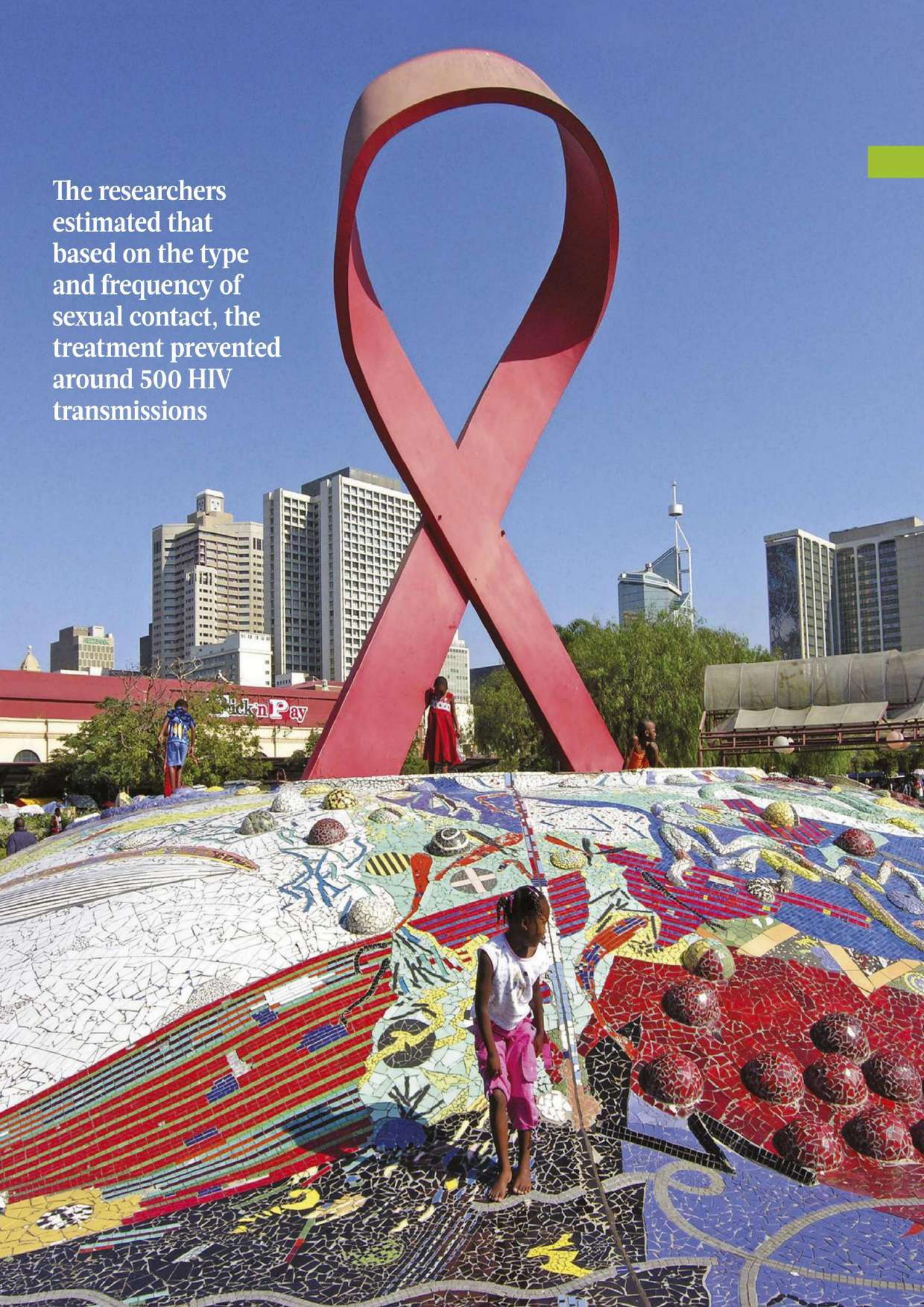
Autoimmune disorders fall into two categories: those that are systemic and damage many organs, such as systemic lupus erythematosus, and those that are localised and affect one organ or tissue, type 1 diabetes, for example, which affects the pancreas.

Autoimmune diseases can affect anyone, but people at greater risk include women of childbearing age, people with a family history of autoimmune disease and those working with chemical solvents, such as cleaners, beauticians and decorators. Symptoms include fatigue, muscle aches and a fever. Treatment includes controlling inflammation and pain, which can be done with drugs, such as ibuprofen.

Some drugs suppress the immune system itself, helping control disease process and preserve organ function. Medicines used to suppress inflammation include those given to recipients of donor organs to protect against rejection. A class of drugs called anti-TNF medications blocks inflammation in rheumatoid arthritis.



Swelling and stiffness in the joints, particularly in the feet, is a symptom of the autoimmune disease rheumatoid arthritis



The researchers estimated that based on the type and frequency of sexual contact, the treatment prevented around 500 HIV transmissions

BREAKTHROUGHS

An end to AIDS is in sight

Conclusive results of an eight-year study find that men on an antiretroviral HIV treatment have a zero risk of passing on the virus to sexual partners

words by JASON GOODYER

An antiretroviral treatment developed by researchers at University College London (UCL) and the University of Copenhagen has reduced the possibility of passing on the virus that causes AIDS to zero.

The study, named PARTNER2, involved nearly 1,000 European gay couples in which one partner was HIV positive and the other HIV negative. Over the course of the eight-year study the couples reported having sex without the use of condoms nearly 80,000 times. None of them was found to pass on the virus to the HIV negative partner. The researchers estimated that based on the type and frequency of sexual contact, the treatment prevented around 500 HIV transmissions.

LOWERING THE LOAD

"Our findings support the message of the international Undetectable = Untransmittable (U=U) campaign, that a suppressed viral load makes HIV untransmittable. This message has been endorsed by more than 780 HIV organisations in 96 countries and can help end the HIV pandemic by preventing HIV transmission, and tackling the stigma and discrimination that many people with HIV face," said lead researcher Prof Alison Rodger of UCL.

Antiretroviral drugs work by stopping a virus from replicating in the body, allowing the immune system to recover and preventing further damage. The measure of the number of viral particles present in a given person's bloodstream is known as a viral load and is expressed as the number of copies of the virus found in one millilitre of blood. For anyone on antiretroviral treatment therapy the aim is to keep the viral load as low as possible.

In the PARTNER2 study, the treatment kept the viral loads of the HIV positive participants at fewer than 200 copies per millilitre, known as an 'undetectable viral load' and is the point at which the virus cannot be transmitted. When not on antiretroviral treatment, viral load among HIV positive patients can reach several millions.

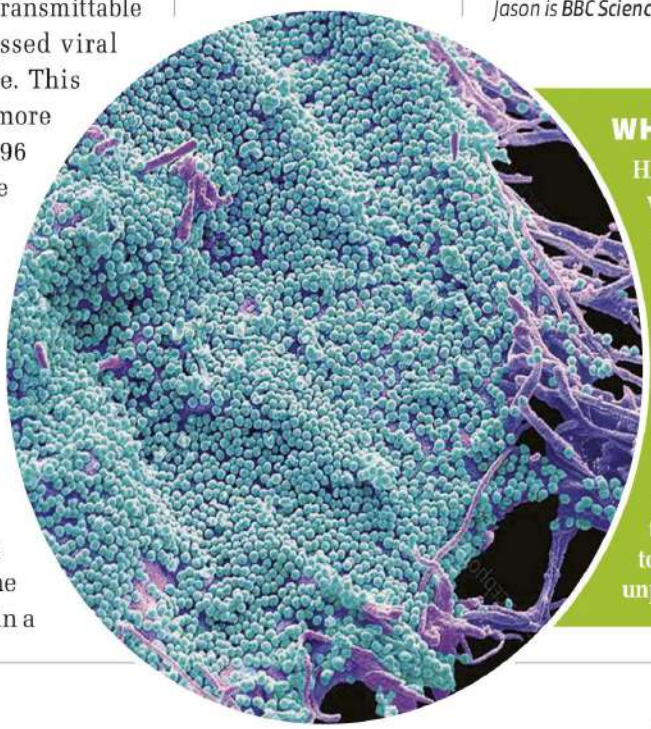
"Increased efforts must now focus on wider dissemination of this powerful message and ensuring that all HIV positive people have access to testing, effective treatment, adherence support and linkage to care to help maintain an undetectable viral load," said Prof Rodger. **SF**

by JASON GOODYER

Jason is BBC Science Focus Magazine's commissioning editor.

LEFT: AIDS ribbon structure in Durban, South Africa

BELOW: Human cell (purple) infected with HIV virus (blue spheres)



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WHAT ARE HIV AND AIDS?

HIV (human immunodeficiency virus) damages cells in the immune system, weakening its ability to fight infection and disease. AIDS (acquired immune deficiency syndrome) describes the potentially life-threatening illnesses that can arise when the immune system has been damaged by HIV. AIDS can't be passed from one person to another, but HIV can be transmitted from an HIV positive to an HIV negative person through unprotected sex or sharing needles.

Muscular SYSTEM

Your muscles are what allow you stand up and move your limbs. They're also what keeps air coming into your lungs, blood pumping around your body and food moving through your gut. But without sufficient work, your muscles will waste away. And while gravity exerts enough of a force on your body to keep your muscles working when you're on Earth, what happens when you go into space?

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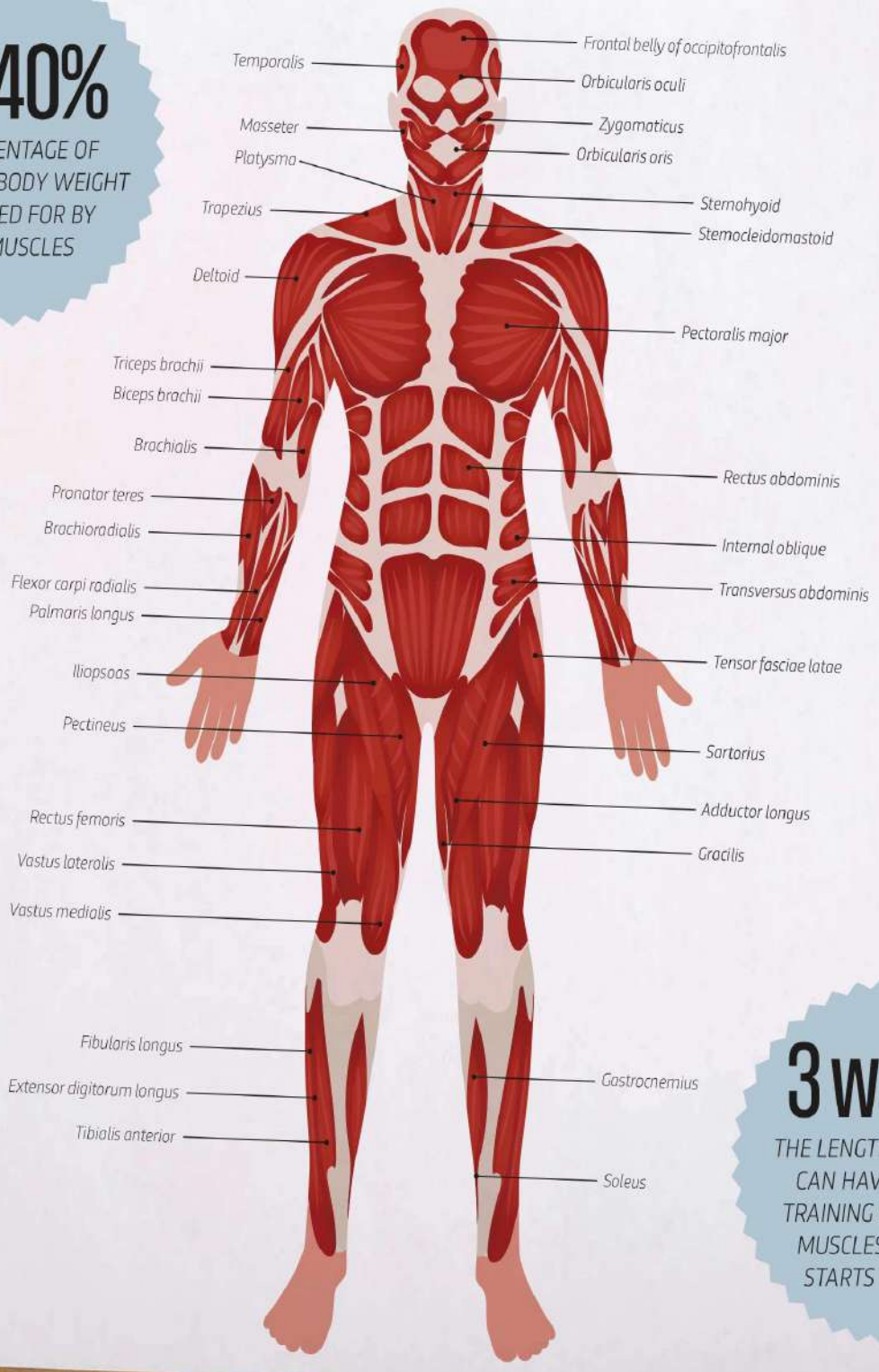
30-40%

THE PERCENTAGE OF YOUR TOTAL BODY WEIGHT ACCOUNTED FOR BY YOUR MUSCLES



3 weeks

THE LENGTH OF TIME YOU CAN HAVE OFF FROM TRAINING BEFORE YOUR MUSCLES' STRENGTH STARTS TO DECLINE

what is this?

American **ASTRONAUT** Mark Vande Hei exercises aboard the International Space Station using the Combined Operational Load-Bearing External Resistance Treadmill (COLBERT). The device was developed to provide a load to the astronauts' muscles while they work out in microgravity.

NASA

FLEX YOUR MUSCLES

Your muscles are lazy. They're all too happy to do as little as possible. But if they're left doing next to nothing for too long, they'll start to deteriorate. And that's when the real problems begin. So how do you get them to keep working when there's nothing for them to work against?

words by HAYLEY BENNETT

Have you ever been bed-bound for a couple of weeks, whether through illness or injury? If so, you probably found it hard to get going once you were up and active again. And if it was any longer than a couple of weeks, you probably felt very weak when you were finally able to get back on your feet. That's because after just a few short weeks of bed rest, the muscles in your body start breaking down.

The thing about muscles is that they're made to lift and carry. "Muscles like load," explains Prof Melinda Sheffield-Moore, head of the health and kinesiology department at Texas A&M University. "And load can be everything from simply standing up, all the way to squatting 300lbs in the gym."

Along with your tendons and ligaments, muscles are the system that your body uses to generate movement, of all kinds. There are tiny, not very well known muscles involved in even the most imperceptible action – the tensor tympani, for example; it's a muscle in your ear that pulls on your eardrum to suppress the sound you make when you chew.

And then there are the big, obvious muscles involved in powerful movements such as sprinting. Your two gluteus maximus muscles, or 'glutes', which make up your backside, are the biggest. These and the 700 or so other skeletal muscles attached to your bones do the body's heavy lifting, while there are other types of muscles that keep your heart and guts functioning (see 'Movement generators', p55).

USE IT OR LOSE IT

About 30-40 per cent of a healthy person's body weight is muscle – women tend to fall at the

If muscles aren't constantly loaded, they can deteriorate rapidly

lower end of that range and men at the higher. But maintaining a healthy percentage depends on keeping your muscles working. If muscles aren't constantly loaded, they can deteriorate rapidly. Studies from New Zealand's Sport Performance Research Institute suggest that rugby and football players can only stop training for three weeks before muscle decline sets in, with strength noticeably tapering off from this point. Even if you're not a professional athlete, taking the load off your muscles by lying in bed for too long will cause your muscles to start wasting away – we see this in patients with advanced cancer, for example.

In fact, bed rest is the approach that scientists researching space travel on Earth take to mimic the effects of zero gravity on human muscles. In a weightless environment, muscles don't have to work as hard, so astronauts have to do around two hours of exercise a day just to keep their muscles at a functioning level. On the International Space Station, for example, astronauts wear a special harness that has bungee ropes to tether them to a running machine. By adjusting the harness they're able to alter how much load they put on their muscles while they run.

"If you don't do [exercise] in space, then the muscle deteriorates to the point that when the astronaut returns to Earth they're unable to walk," says Prof Sheffield-Moore. This could put them in danger – for example, if there was an emergency during landing and they had to evacuate the return capsule quickly. Even with rigorous in-flight training, astronauts come back to Earth weaker – calf strength, a good marker of skeletal muscle loss, decreases by over 10 per cent during a mission.

Prof Sheffield-Moore is one of the scientists conducting bed rest research funded by NASA. She was recently involved in a study that saw 27 men consigned to bed for 10 weeks, with one group lying down the whole time, a second group only getting up to exercise and a third also able to exercise but given low-dose injections of the hormone testosterone. Exercises included using a vertical treadmill, which suspends the test subjects from the ceiling in a horizontal position, so that they can walk or run facing upwards – this removes much of the load, creating a similar effect to running on a treadmill in space.

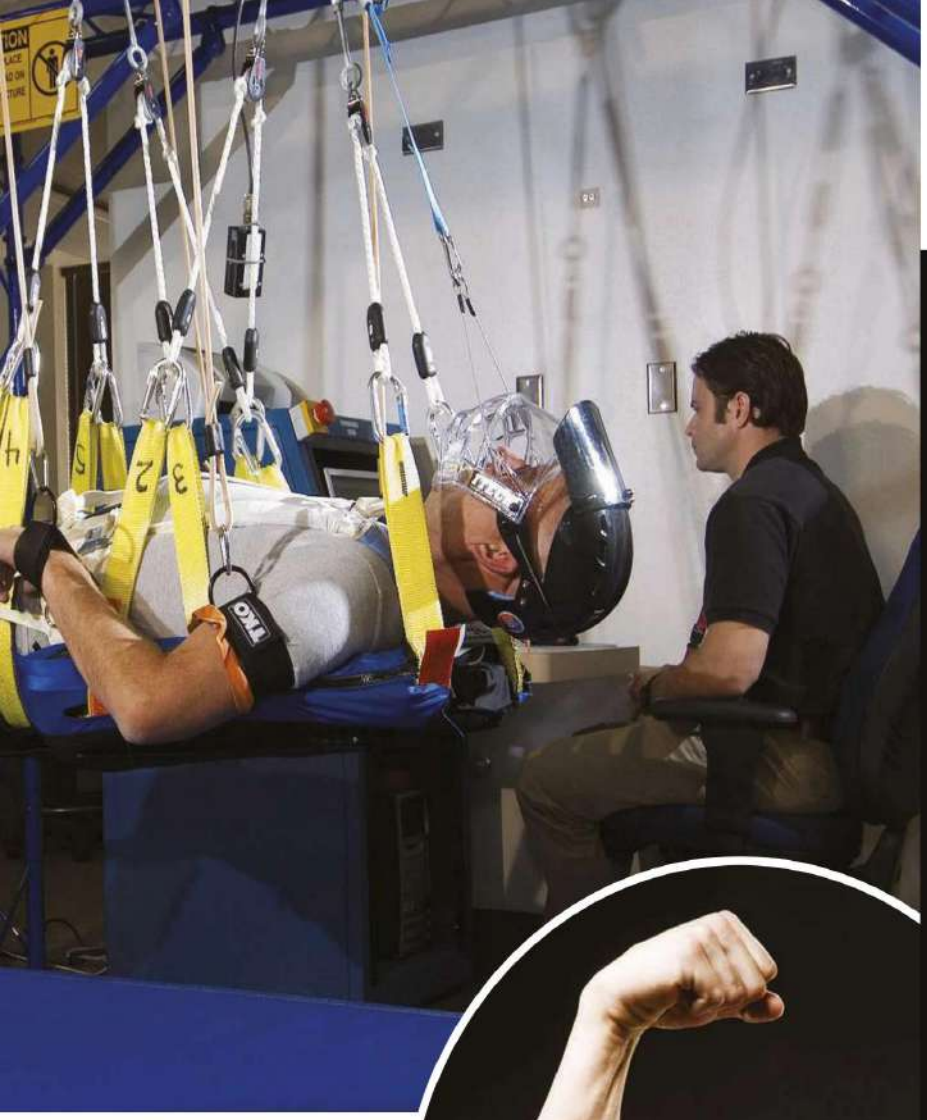
Prof Sheffield-Moore and her team tested the study participants' strength by measuring

ABOVE LEFT: Regaining the strength to walk can take time if you've been confined to bed for an extended period of time

ABOVE: The NASA-funded 'bed rest' study investigated how specialised exercise equipment can be used to counteract the muscular degeneration caused by being in space

RIGHT: The right balance of work load and protein consumption can generate extreme muscle growth

GETTY IMAGES X5, NASA



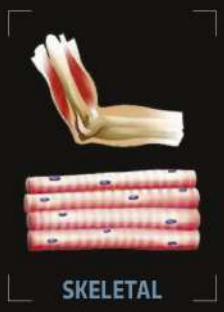
two types of muscle contractions: concentric, or muscle-shortening contractions, which change the angle of a joint such as the knee or elbow; and eccentric, which control the lengthening of the muscle while under tension, such as when bracing to lift a heavy weight. When they were finally let out of bed, those in the group that did no exercise had lost on average 30 per cent of the eccentric strength in their calf muscles and 24 per cent of the concentric strength. The exercising group had losses of 14 and 11 per cent respectively, while the group that exercised and was given testosterone injections minimised losses to three per cent for both types of muscle strength.

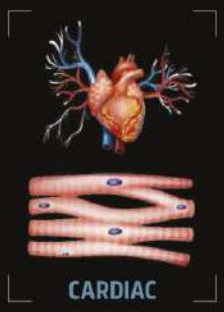
Of course, it's not surprising that testosterone has beneficial effects for astronaut's muscles, given its widespread use by drug cheats in sports. But these improvements were achieved by injecting low doses of the hormone straight into the muscle, without raising the overall ➤

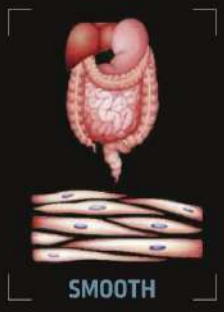
MOVEMENT GENERATORS

Skeletal, cardiac and smooth – different muscles for different purposes

SKELETAL MUSCLE is the muscle attached to your bones that enables you to move. It is the only type of muscle that allows you to consciously move parts of your body. We call these movements voluntary movements, such as when you use 12 of the 42 muscles in your face to smile. The other type of movement is involuntary movement. Our skeletal muscles do both. So when your diaphragm moves downwards to make space for you to inhale air, it's skeletal muscle that's causing it to contract without you having to think about it, although you can.

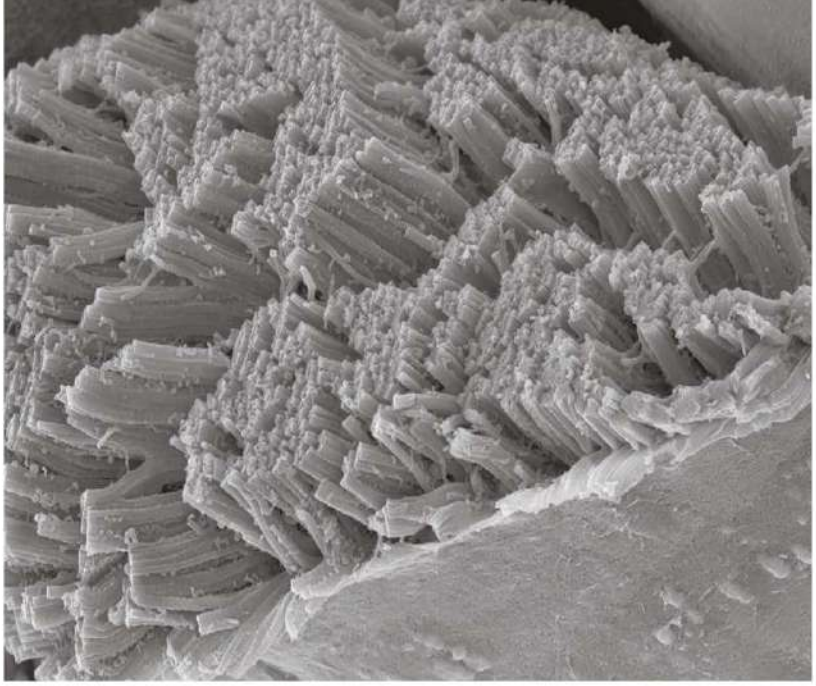






The actions of other types of muscles, however, are completely involuntary. Your solitary **CARDIAC MUSCLE** – the heart – can't be consciously controlled and neither can the muscles that pump blood through your blood vessels. The blood-pumping muscles are the third type: **SMOOTH MUSCLES**. These are the type of muscles found in your organs and that keep your guts moving. Contractions in the lining of the gut form tight rings that literally squeeze the food through. Though you don't even know they're there, if anything goes wrong with smooth muscles, it can be disastrous. An error in a particular gene called ACTA2 causes all the body's smooth muscles to fail, resulting in serious problems with digestion and blood vessel abnormalities. Duchenne muscular dystrophy, by contrast, affects all three types of muscles, with patients sometimes showing skeletal muscle weakness first, followed by smooth muscle problems and heart failure.

Hibernating bears do not suffer the same fate as humans when they lie down for a long time



Severed skeletal muscle fibres seen under a scanning electron micrograph

GETTY IMAGES X3, NASA

level of testosterone in the blood above that of the participants who didn't have the injections. Prof Sheffield-Moore says these are the types of doses that are given to cancer patients and older people to improve their quality of life – it gives their muscles a little boost to allow them to carry on doing simple activities, such as cooking and going to the bathroom.

THE PROTEIN PUZZLE

Skeletal muscle cells are stuffed full of proteins, hence the reason weightlifters take protein supplements to build muscles. Some of these proteins form the structural components of muscle fibres responsible for contracting and relaxing to generate movement. The best known are the muscle proteins, actin and myosin. But there are a whole raft of others involved in growing, controlling and supporting the actions of muscle cells. There are also many proteins involved in metabolic processes. These too have to be maintained in space, as it's unclear if losing them could have long-term effects on astronauts' metabolisms, possibly even resulting in chronic disease later down the line.

The sum of all of the proteins in the muscle is called the muscle proteome. "It's this big puzzle of proteins – all different types," says Prof Sheffield-Moore. Like a puzzle, the pieces can be popped in and out. It's a dynamic entity. So while muscle is a great reservoir for proteins and their sub-units, amino acids, it's easily depleted if we stop eating, for example. The body can recycle the amino acids to generate fuel. What happens in zero gravity or when someone is bed bound also changes the make-up of the muscle proteome, in line with measurable muscle loss. Some pieces of the puzzle are lost or just don't fit any more.

When Prof Sheffield-Moore's team took muscle biopsies from their study's participants, they found that a particular set of proteins became less active following full bed rest, while the same proteins remained active in those who exercised. These included proteins that bind to some of the important structural components of muscle fibres and one that may be involved in determining what type of cell a muscle cell becomes while it's developing. The proteins active in the test subjects who were given testosterone were different again, perhaps explaining testosterone's muscle-preserving effects.

Far from 'jacking up' astronauts, adding testosterone to their zero-gravity exercise programmes could help keep muscle loss in space to a minimum. But from NASA's perspective, it's also a time-saving solution, explains Prof Sheffield-Moore. "They want to do these longer-term space flights and they can't have their astronauts exercising two thirds of the day in order to maintain muscle mass," she says. Astronauts need to be working on science, not just working out.

There may be other avenues worth investigating in pursuit of preserving muscle mass, though. For instance, we know that hibernating bears do not suffer the same fate as humans when they lie down for a long time. In fact, they can spend half the year resting without losing very much muscle. Scientists are still trying to understand how they do this. One research team suggested that intense shivering may help to prevent their muscles atrophying. The next step: sending a bear into space? **SF**

Developments in prosthetic limb technology could see them more closely mimic the function of the biological limbs they replace

Added power

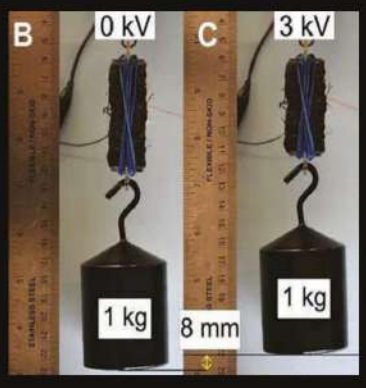
A prosthesis can replace a lost limb but not the muscles in it... until now

You've heard of artificial hips, knees and limbs. But what about artificial muscles? Think about it: if you lose the lower part of your leg, you can replace the bone with a piece of titanium or even carbon fibre. But how do you replace the muscles that powered that leg?

In most cases, you don't. The prosthesis isn't powered at all, except by the energy the rest of the leg puts in. A Paralympic sprinter doesn't use a battery to power their blade, so the blade must be made in such a way that the materials can utilise as much of the energy transferred from the rest of the body as possible.

Now, though, researchers are working on artificial muscles to power the next generation of artificial limbs, and not just for amputees – for robots as well. The difficulty they have in doing this is getting a lot of power out of something the size and weight of a real muscle. Traditionally, robots capable of lifting heavy loads have weighed in pretty heavily themselves and if you're already carrying around a prosthesis, you don't want to be dragging along a power pack the size of a car battery to run it.

To solve the problem, scientists have been taking inspiration from nature. Many are now using soft materials, such as electroactive polymers, which change shape and size in response to an electric current but don't weigh a huge amount. There have also been slow-twitching prototypes based on twisting together slender synthetic threads in such a way that they contract and relax in response to temperature changes and are capable of lifting up to 7kg. Most recently, researchers at Harvard University used very thin, very strong materials called elastomers to create artificial muscles that contracted as fast as natural muscles when supplied with electricity. **SF**



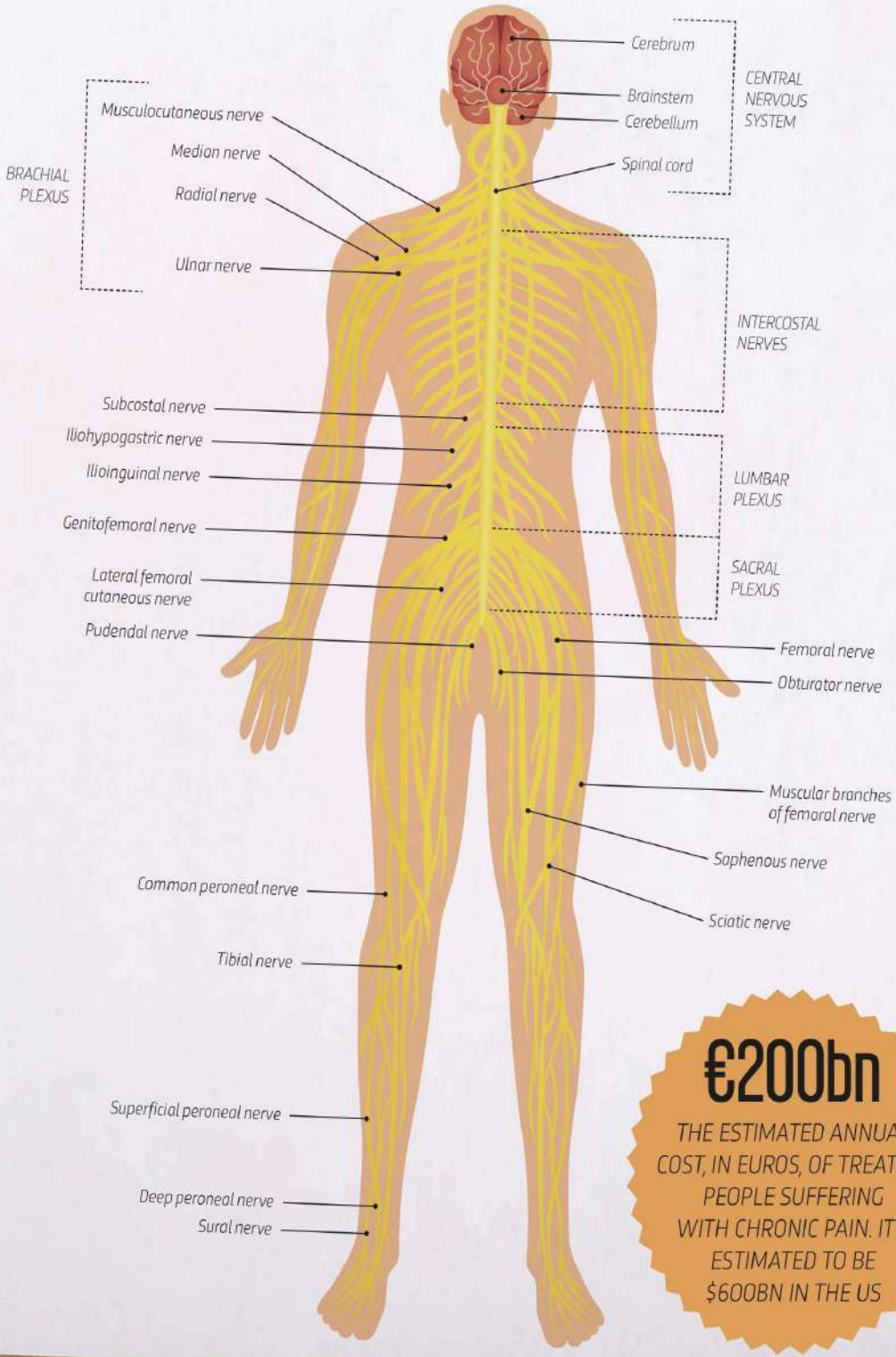
The artificial muscle can lift a 1kg weight when an electric field is applied

by **HAYLEY BENNETT** *(@gingerbreadlady)*
Hayley is a science writer specialising in biology, chemistry and the environment. She is one of the authors The Big Questions In Science.

Nervous SYSTEM

When you touch something, nerve receptors in your skin detect where and how the contact was made and relay that information, through your nervous system, to your brain so it can generate the appropriate response. If it's something pleasant, such as stroking a cat, you get a sensation of pleasure. But if it's something unpleasant and potentially damaging to your body – picking up a hot pan perhaps – you feel pain. What's amazing, though, is how your nervous system can tell the difference

GETTY IMAGES X2, VECTORSTOCK



€200bn

THE ESTIMATED ANNUAL COST, IN EUROS, OF TREATING PEOPLE SUFFERING WITH CHRONIC PAIN. IT'S ESTIMATED TO BE $600BN IN THE US

THE PATHWAY OF PAIN

Everybody hurts, but how does your brain detect the discomfort?

words by PROF IRENE TRACEY

We may have learnt to tame it with drugs, but pain is one of the certainties of human existence. It can be both physical and emotional, ranging from a searing torment to a mild soreness. But what is it, what function does it serve, and how can we really know how much pain someone is in?

WHAT IS PAIN?

Mostly, it's a brilliant warning system. Without it, you wouldn't withdraw your hand when you grab a hot pan, and the burn would be much worse. Pain like this – acute pain – is a good thing: it's key to your survival. That's why the ability to experience pain is shared across species. A few people include plants in this, but as plants have no nervous system or brain, it's hard to know how they'd feel pain.

Without pain, you're in trouble. We know this, sadly, because there's a rare genetic condition, called 'congenital insensitivity to pain' or CIP, in which a person doesn't get the warning 'hurt' of pain after severely damaging themselves. Historically, they didn't survive to adulthood due to the consequences of unfelt injury.

WHAT DOES PAIN DO?

Pain motivates you to act. Think about that hot pan again. Imagine you'd picked it up before realising it was too hot to handle. Your options are to drop it and make a mess, or bear the pain until a solution is found. In an instant, you detect that the pan is hot (thermal), it's on your hand (location), it's painful (intensity), you don't like it (unpleasant), it's engaged your full attention (cognition) and you're not happy about it (emotional). That's a lot of things, which is why pain is said to be a 'multidimensional' experience.

So, what do you do? Well, from past experiences, learnt responses and potential outcomes (such as being told off for dropping the pan) you make a decision and act. Recruiting extraordinary brain-based networks, you're able to block the pain and get the hot pan to safety, then run your hand under the cold tap. In short, pain drives action.

GETTY IMAGES

BBC WORLD SERVICE

Listen to Prof Irene Tracey explain how we experience pain in *The Life Scientific*
bbc.in/2Ms8iAv

HOW DO I FEEL PAIN?

Just beneath your skin surface, is an intricate network of 'pain nerve fibres' that end with special receptors called nociceptors. When activated, nociceptors send signals along the nerve fibres to your spinal cord and up into your brain, where pain, as a perception, emerges.

The nociceptors can be activated by a variety of triggers: thermal (heat), mechanical (a knife cut or hammer blow) and chemical/irritant (acid or chilli pepper). The signals then travel along different types of pain nerve fibre. A-delta fibres carry what we call 'first pain' – the fast, quick signal that tells you 'ouch' when you touch a hot pan. C fibres follow up with the 'second pain', which is the slow throbbing that tells you it still hurts. Normal touch – feeling something like your clothes or holding a pen – is carried on different peripheral A-beta nerves.

Interestingly, many nociceptors are 'polymodal' – meaning that different things can activate the same nociceptor, temperature and food for example.

HOW CAN FOOD BE PAINFUL?

Different thermal nociceptors in your body are activated by specific temperatures, giving you a painful sensation of intense hot or cold. Amazingly, these same nociceptors are also activated by various natural chemicals, giving rise to the same experience. For instance, when you bite into a chilli pepper, a chemical called capsaicin binds to the same nociceptor that's activated by painfully hot temperatures of around 42°C and above. That's why you perceive a curry as hot: your brain can't distinguish what activated the nociceptor, it just knows that your mouth is burning.

HOW DOES THE BRAIN GENERATE PAIN?

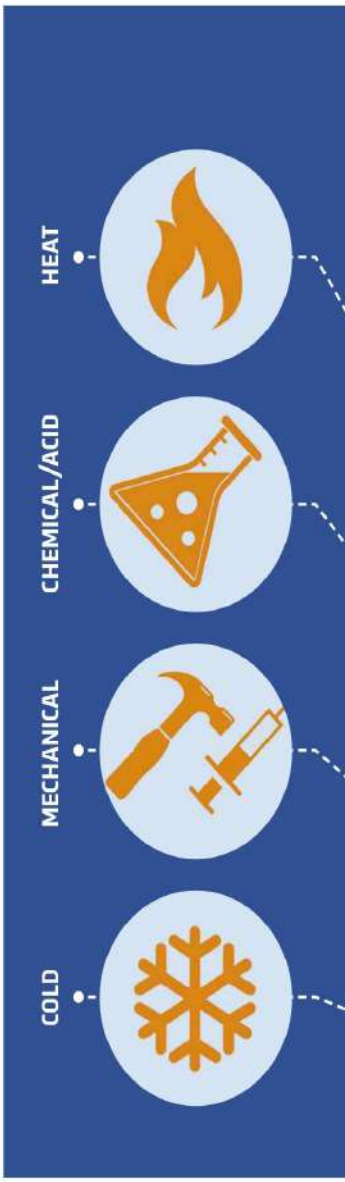
Once the pain signals arrive at the brain, a large network is activated, which includes the brain stem, the thalamus and several regions of the cortex. The experience of pain then emerges from this activity. Until the conscious brain processes these incoming signals, we don't actually call it pain, but nociception – this is the nervous system's response to the original tissue damage. The relationship between the extent of tissue damage and the amount or quality of pain that you actually feel is not a simple one-to-one mapping. Incoming signals can be amplified, attenuated or reappraised by your brain, which can dramatically change your experience of it. So, being anxious about your pain at the dentist really will make it worse – emotions are like amplifiers in your brain, turning up the volume of pain.

CHRONIC PAIN IS DEFINED AS PAIN THAT PERSISTS BEYOND THE NORMAL TISSUE HEALING TIME

Thankfully, you also have a built-in system to lessen pain. The brain system that's responsible for the feelings of pain can talk to the spinal cord and suppress nociceptive signals, like a brake. This results in less brain activity and less pain, at least until the brake is removed. This is what goes on in athletes and soldiers during situations of high arousal and battle, or when someone is distracted from their pain (for example, a parent desperately distracting their child from the dreaded vaccine jab). It's not a trick, but real physiology. In fact, it's this system, called the 'descending pain modulatory system', that's hijacked when the placebo effect acts to reduce pain. This is known as 'placebo analgesia'.

WHAT IS CHRONIC PAIN?

This is the system gone wrong. It's defined as pain that persists beyond the normal tissue healing time. One in five adults experiences it. It lasts, on average, for seven years, but for 20 per cent of people it's more than 20 years, and is more prevalent in women and the elderly. Chronic pain wreaks suffering on patients and their families. It also brings significant costs to society, estimated annually at €200bn in Europe and $600bn in the US. Depression, anxiety and sleeplessness can add to the suffering.

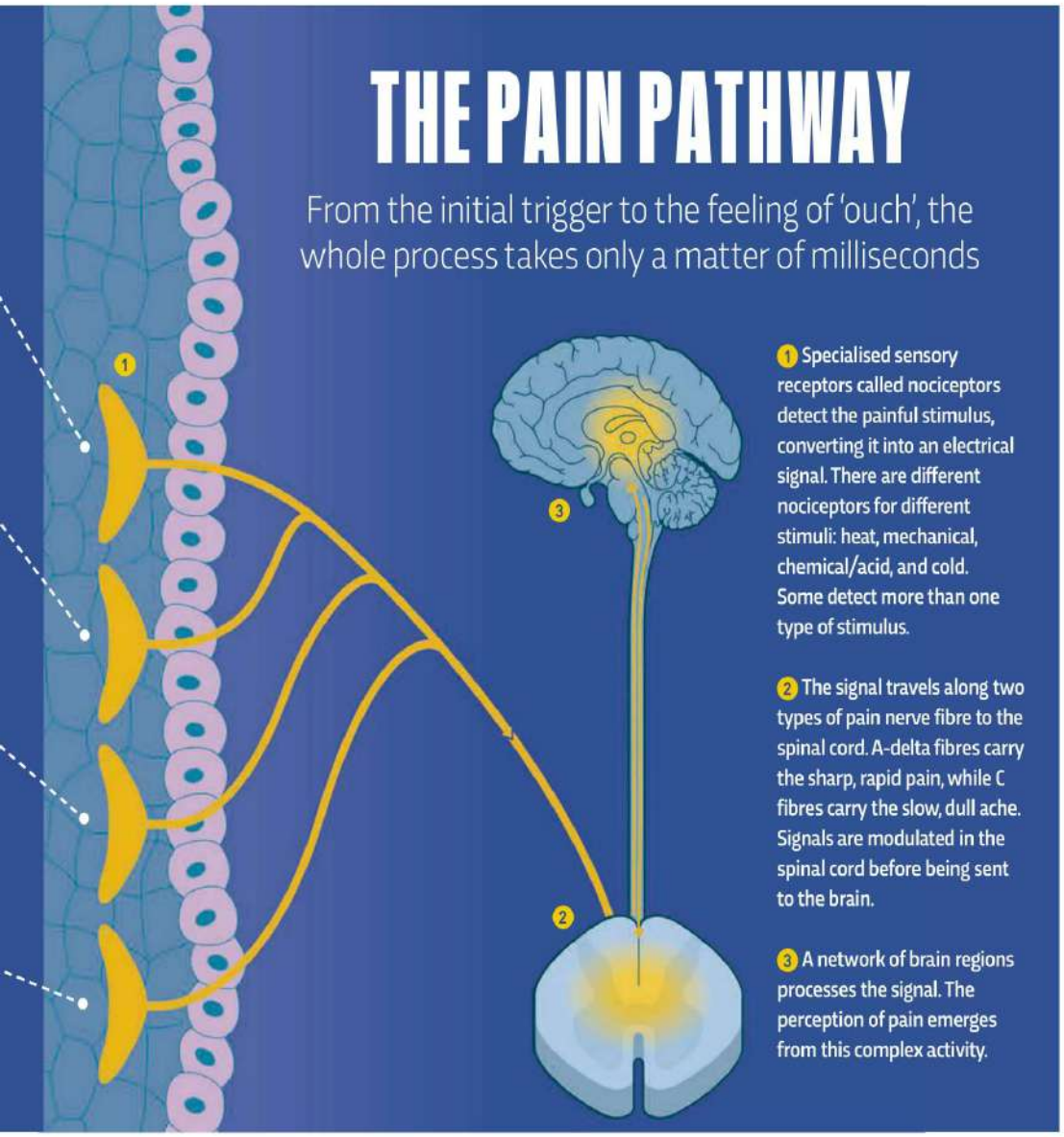


Capsaicin in chillies binds to heat receptors in your mouth, which is why spicy food burns

ILLUSTRATION: ACUTE GRAPHICS, GETTY IMAGES

THE PAIN PATHWAY

From the initial trigger to the feeling of 'ouch', the whole process takes only a matter of milliseconds



1 Specialised sensory receptors called nociceptors detect the painful stimulus, converting it into an electrical signal. There are different nociceptors for different stimuli: heat, mechanical, chemical/acid, and cold. Some detect more than one type of stimulus.

2 The signal travels along two types of pain nerve fibre to the spinal cord. A-delta fibres carry the sharp, rapid pain, while C fibres carry the slow, dull ache. Signals are modulated in the spinal cord before being sent to the brain.

3 A network of brain regions processes the signal. The perception of pain emerges from this complex activity.

Chronic pain is one of the largest health problems worldwide and current treatment options do not provide adequate relief to the majority of patients. Patients with chronic pain might have different conditions. Nerve damage due to diabetes, being on chemotherapy, multiple sclerosis, sustaining an injury, phantom limb pain, or arthritis, are a few examples. Yet the signs and symptoms that patients describe are often similar. We're starting to consider chronic pain as a disease, with underpinning problems that we can work on and try to fix.

A key problem in chronic pain is that A-delta and C fibres can switch on permanently when damaged, sending constant pain signals to the sufferer's brain. Second, it's been shown that the pathway from nociceptor to brain can get 'sensitised' so that the signals are amplified. This makes the situation worse, causing even the touch of clothing or bedsheets to become painful.

jargon buster

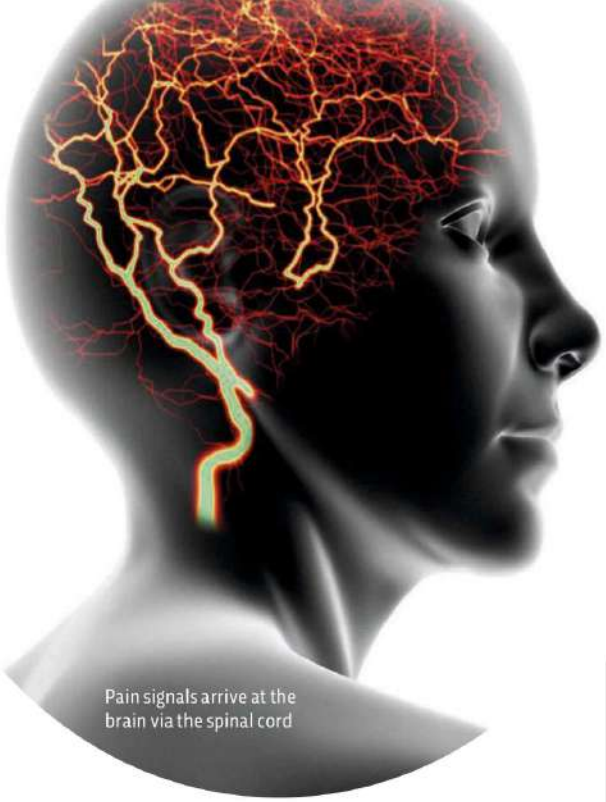
CAPSAICIN
This chemical, found in chillies, binds to a nociceptor that responds to extreme heat. This is why biting into a chilli can cause pain.

NOCICEPTORS
These are receptors on the pain nerve fibres that act like a lock. Certain keys (irritants, mechanical forces, temperature) open them and set off messages to the brain, signalling pain and tissue damage. Over-the-counter painkillers target nociceptive pain.

PAIN NERVE FIBRES
A-delta and C fibres are nerves that carry signals from nociceptors in the skin, muscles and joints to the spinal cord.

PHANTOM PAIN
This is the perception of pain in a limb or organ that's missing. It often occurs following the amputation of an arm or a leg. It's devastating for patients, and some theories suggest that it's a result of altered nerve signals in the brain trying to 'fill the gap'.

PLACEBO ANALGESIA
Placebos are substances with no active therapeutic effect. Patients who take them often report improvements in their condition. Placebo analgesia is pain relief from, say, a sugar pill, and neuroimaging has shown that it can work by hijacking an old and built-in 'free pain relief' system in the brain.



Pain signals arrive at the brain via the spinal cord

SOME STUDIES SUGGEST WOMEN ARE MORE SENSITIVE TO PAIN THAN MEN, BUT PERHAPS WOMEN COPE BETTER WITH IT

HOW CAN SOMEONE KNOW HOW MUCH PAIN I'M EXPERIENCING?

It's important to let others know when you're in pain, partly because this drives empathy and compassion in the people around you, but also because doing so elicits their help in treating the cause of it. Generally, we use behavioural observations and language to work out if someone is suffering. People grimace, writhe or cry out in agony. But it's difficult to measure pain, as it's such a subjective experience.

If language is available, then rating scales can help to capture features of the pain such as intensity and unpleasantness (0 = no pain, 10 = excruciating). Questionnaires can be used instead of number scales and sometimes just smiley or sad faces, which are useful if you're dealing with children. Pain levels of babies, comatose or anaesthetised individuals, or dementia patients may be more difficult to judge and it's tough to know what they're really feeling. Looking at body measures, like heart or breathing rate, can help. Some studies suggest that women are more sensitive to pain than men, but perhaps women cope better with it. Brain imaging is helping us to understand pain better, but it should not be used as a surrogate for what the person reports. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". In short, if someone says they're in pain, then they are, no matter what caused it.

HOW DO WE TREAT PAIN?

Painkillers provide relief from pain. The two oldest are aspirin, which is derived from willow bark, and morphine, which comes from opium poppies. These days, aspirin is largely replaced by ibuprofen if there is inflammation, or paracetamol if there is no inflammation. Morphine is an opioid and variants of it are still used, but can have associated problems like tolerance and addiction. Other painkillers include different types of anti-inflammatory style drugs, antidepressants, and anticonvulsants. There are many additional treatments for pain, including cognitive behavioural therapy, physiotherapy and surgery, and the most effective therapies combine all of these treatments. With new drugs coming through the pipeline, and our understanding of pain constantly improving, we can hope for a future where no one will have to suffer unnecessary pain. **SF**

by **PROF IRENE TRACEY** *is head of the Nuffield Department of Clinical Neurosciences at the University of Oxford.*

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WHAT WE STILL DON'T KNOW

1 HOW WE DETECT A PINPRICK

Using molecular biology and various natural chemicals as 'probes', we've identified most of the nociceptors in the body that respond to painful events. However, we're still missing the nociceptor that detects a painful hammer blow, knife cut or pinprick. Several research groups are on the hunt for this elusive nociceptor.

2 WHY PEOPLE DEVELOP CHRONIC PAIN

In chronic pain, the A-delta and C fibres often switch on permanently, causing non-stop agony. If we can work out why this happens and prevent it, we could help millions of sufferers. Also, we still need to understand why, after the same injury, one person can develop chronic pain, but another person does not.

3 WHERE THE 'HURT' IS IN PAIN

It's thought that Oscar Wilde once said: "I don't mind pain, so long as it doesn't hurt". Funny, yet spot on. We know that the perception of hurt emerges from various brain regions activating together, but we don't know how this activity produces the 'hurt' of pain. Brain imaging should tell us more...

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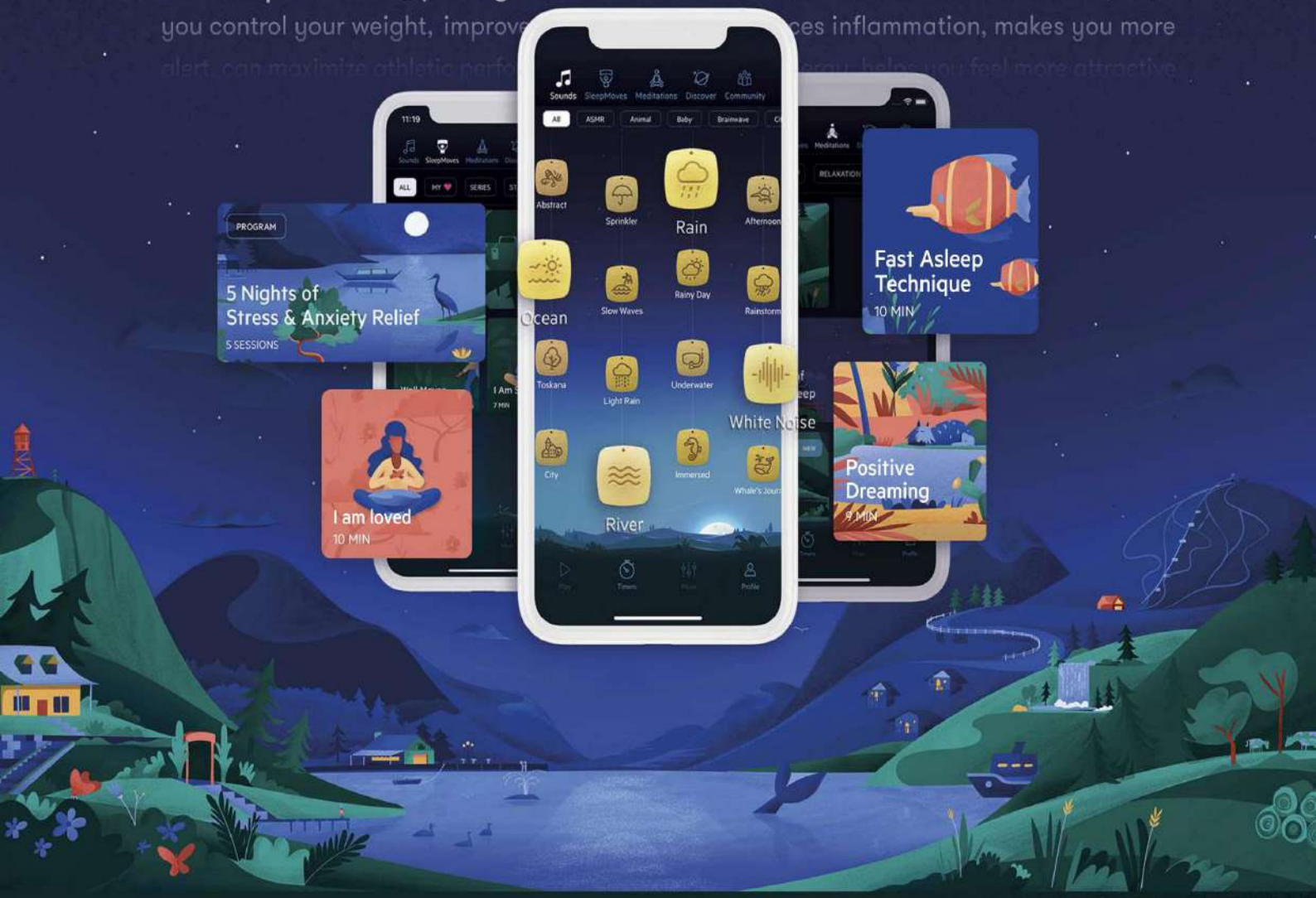

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Renal SYSTEM

Water makes up approximately 60 per cent of the typical adult human body. It's absolutely vital for keeping you alive and having too much in your body is just as dangerous as having too little. Which is why your renal system is responsible for maintaining the right balance by filtering fluid out of your body and releasing it as urine. But it does more besides merely regulating your body's liquid levels

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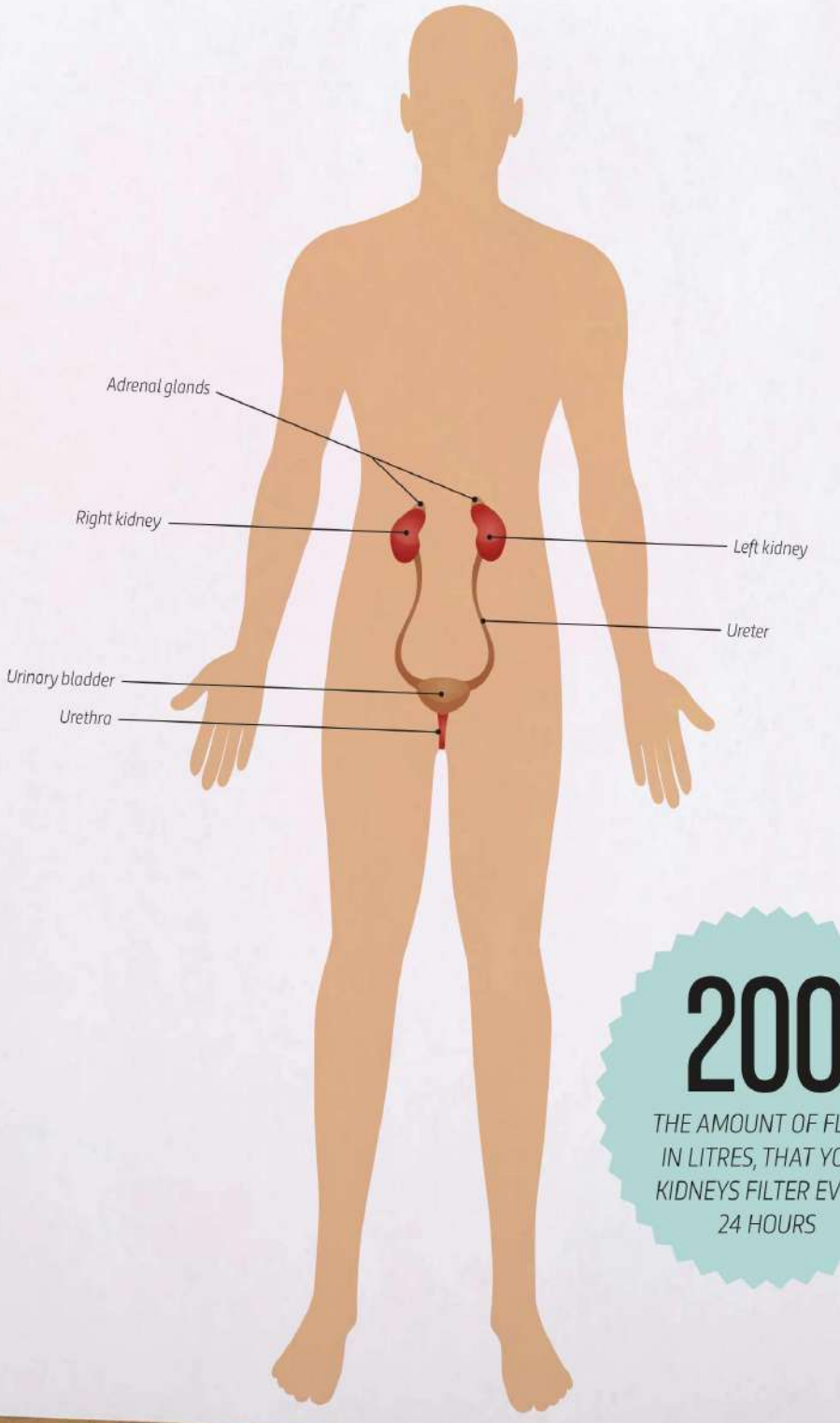
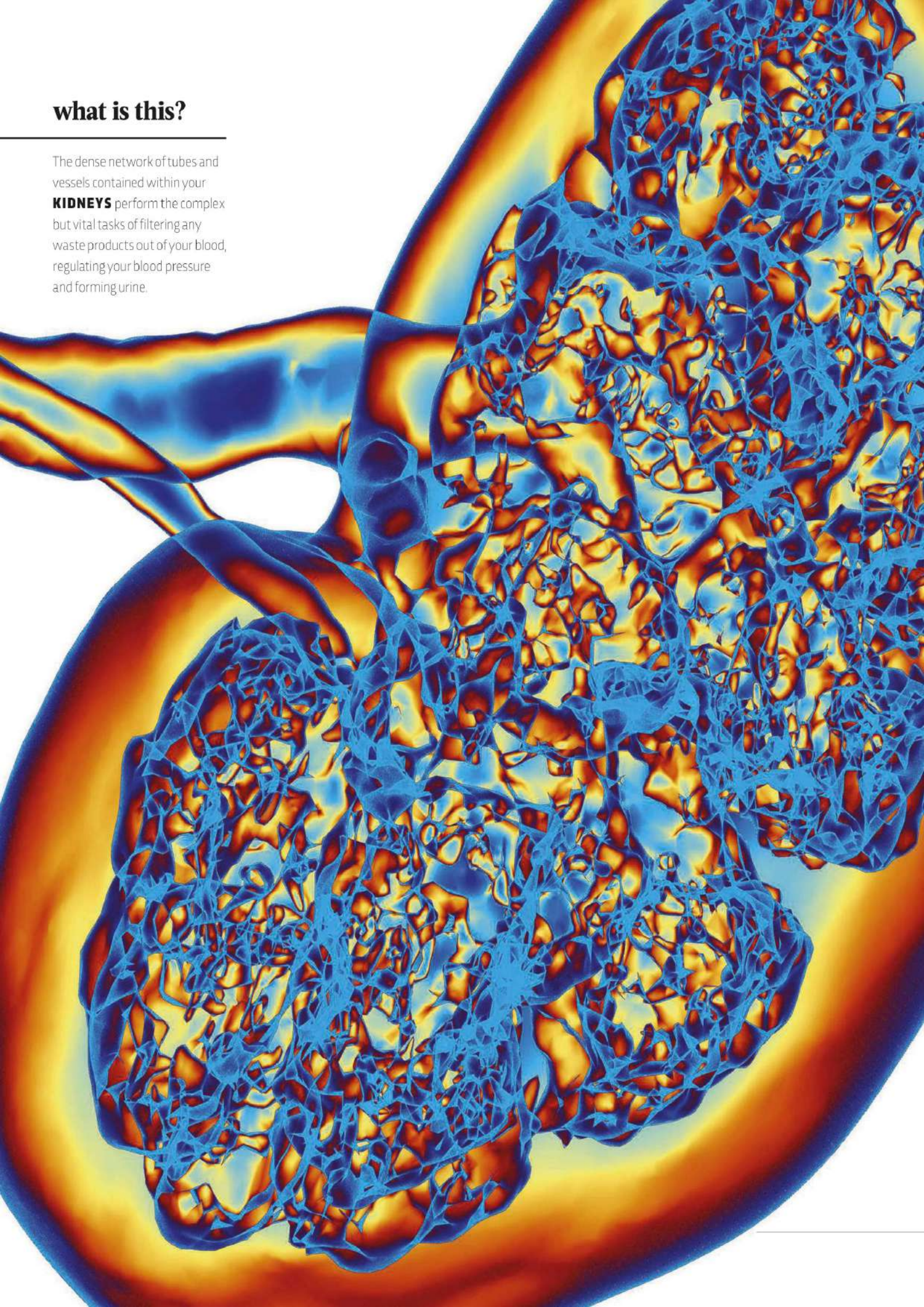


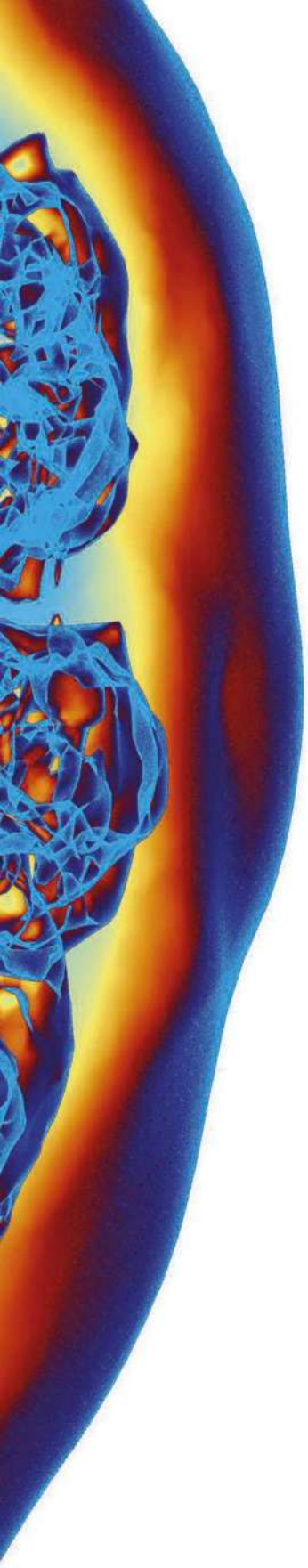
200

THE AMOUNT OF FLUID, IN LITRES, THAT YOUR KIDNEYS FILTER EVERY 24 HOURS

what is this?

The dense network of tubes and vessels contained within your **KIDNEYS** perform the complex but vital tasks of filtering any waste products out of your blood, regulating your blood pressure and forming urine.





GETTY IMAGES

STRIKING THE RIGHT BALANCE

Your kidneys are at the heart of your renal system and they're working constantly to ensure you have just the right amount of water in your body. And while that's not as simple as it sounds, it's also far from the only job your kidneys do

words by DR SALEYHA ASHAN

Your kidneys are like two factories that never stop working. Even while you sleep, they're hard at work filtering your blood and producing urine, which is sent to the bladder. That's why, when you wake up, the first thing you usually want to do is go to the toilet.

These fist-sized, bean-shaped organs sit at the back of your abdomen on either side of your spine. Most people have two kidneys and they conserve or discard water depending on need. Two things make these functions possible: nephrons, the microscopic filtering structures within the kidneys, and anti-diuretic hormone (ADH), which is secreted by the pituitary gland at the base of your brain. If no ADH is present, then more water passes through the nephrons to form urine. If ADH is present, water is absorbed back into your body.

More ADH is secreted at night so that although your kidneys are still hard at work producing urine, you don't need to keep getting up to go to the loo. Also, not drinking – due to being asleep – means you're not producing as much urine as you would during the day, but what you do produce is more concentrated, indicated by the darker colour you see when you do eventually go to the toilet.

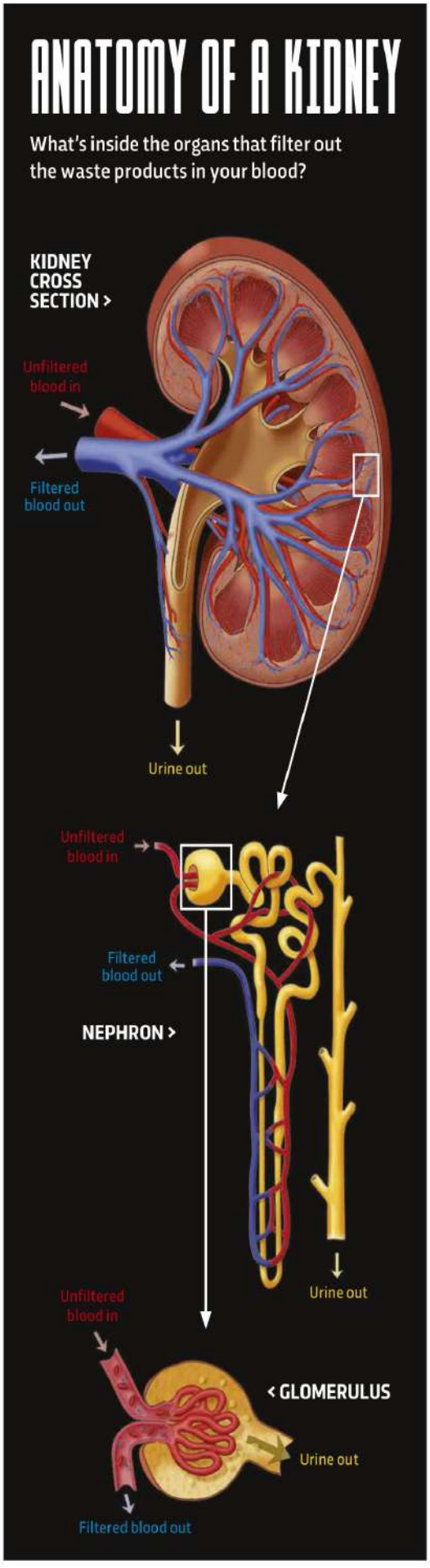
The release of ADH is related to sodium levels in your blood. If your blood has a high sodium level, then ADH is secreted to help you conserve water; if your blood's sodium level is low, very little ADH is released and you pass more urine. Maintaining a fine balance between electrolytes, such as sodium and water, is crucial for cellular function, which is to say it's essential to life; hence the role of your kidneys is vital.

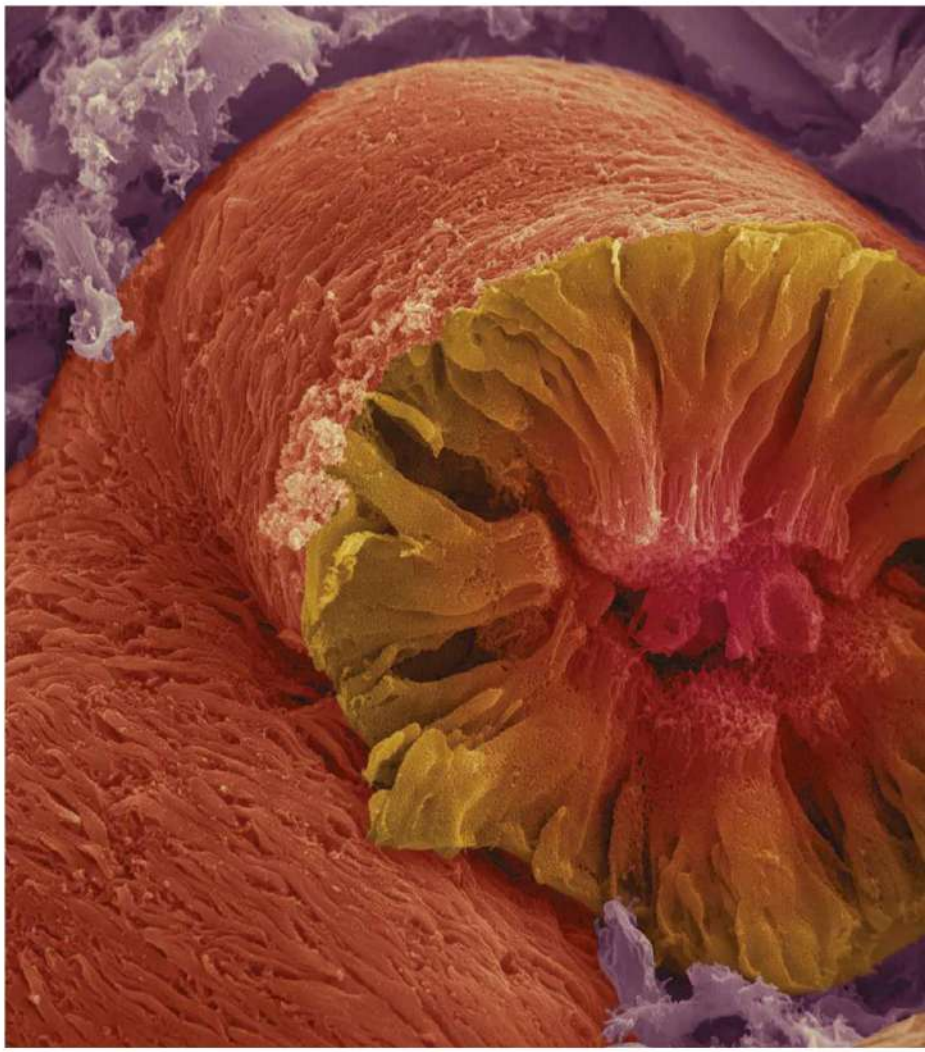
CLEANING AND SCREENING

Day and night, your heart pumps blood around your body. In the process of circulating, it enters your kidneys where it is cleaned by passing through millions of nephrons. Healthy kidneys filter about a half cup of blood every minute, producing urine that passes through two ureters (thin tubes of muscle) to the bladder, where

ANATOMY OF A KIDNEY

What's inside the organs that filter out the waste products in your blood?





ABOVE: The tubules in each nephron absorb useful substances and any necessary water from the fluid passing through your kidneys. What's leftover forms urine

ABOVE RIGHT: Macula densa cells monitor the levels of sodium in the fluid your kidneys are filtering so your blood pressure can be adjusted accordingly

it's stored for between one to eight hours until you urinate. Each nephron includes a filter, called a glomerulus, and a tubule. The glomerulus is a network of small blood vessels with thin walls that allow molecules of waste and fluid (mostly water) to pass into the tubule. In the tubule, sodium, potassium, proteins and most of the water are re-absorbed back to your blood via a vessel that runs alongside it, leaving waste products behind in the filtered fluid, forming urine. Newly cleaned blood returns to the bloodstream.

Your kidneys receive 20 per cent of the total blood volume pumped by your heart, enabling them to regulate its composition. That equates to filtering 200 litres of fluid every 24 hours; only one to two litres leave your body as urine.

In the morning, when you reach for that first cup of coffee or orange juice, you'll probably need to pass urine within about an hour of consuming that drink. That's because your renal system will have detected the extra fluid has been introduced; fluid that has passed through the

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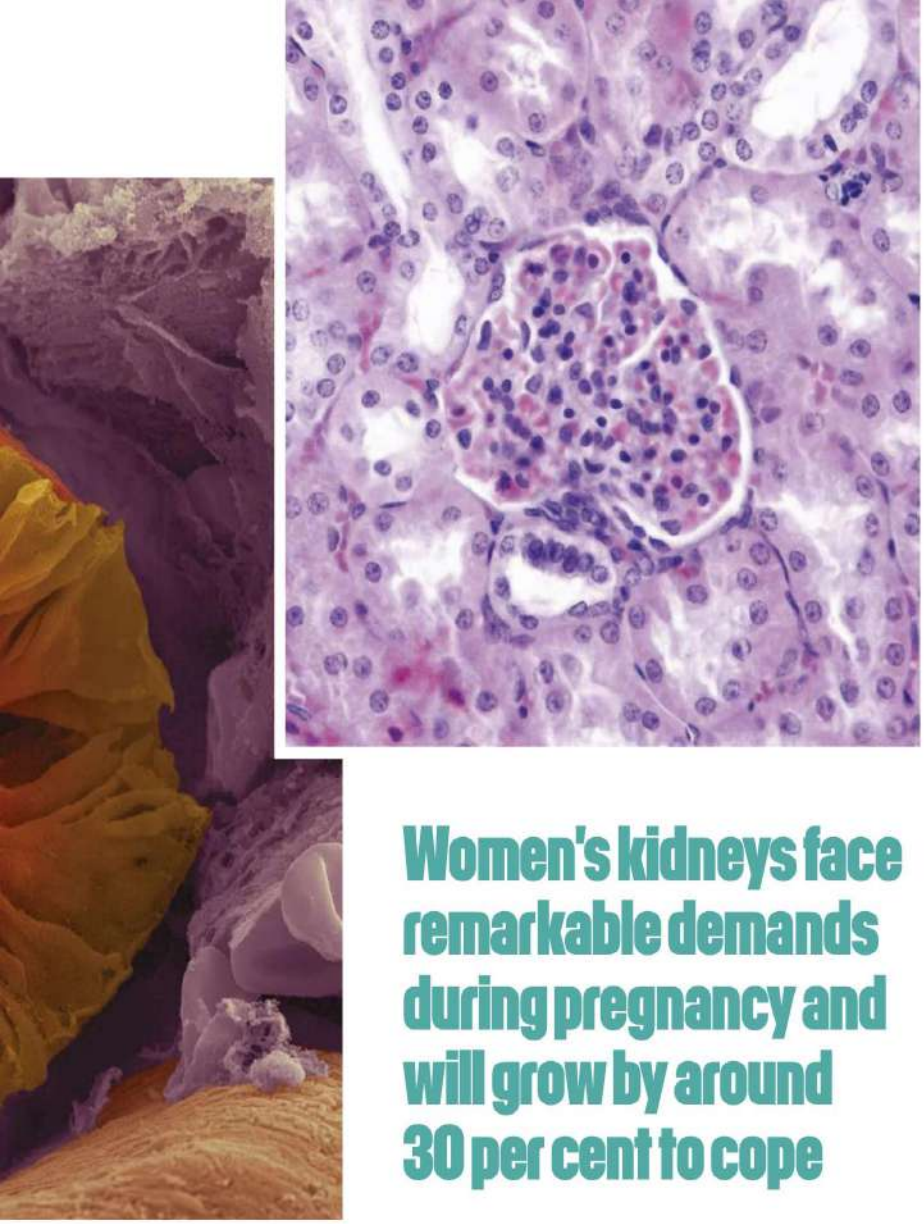


Women's kidneys face remarkable demands during pregnancy and will grow by around 30 per cent to cope

nephrons so the nutrients and water it contains could be absorbed into your body while any excess fluid and waste can be removed and transported to your bladder.

Because you have more fluid on board after drinking, you're 'more dilute' – your blood's sodium level is reduced. Your pituitary gland senses this and secrets less ADH so less water is absorbed. The excess water gets excreted in urine and your blood sodium concentration returns to normal.

Your kidneys also influence your blood pressure by causing arteries and veins to constrict and by increasing volume of circulating blood. Specialised cells, called macula densa cells, in the tubules sense the level of sodium in the filtrate, while another set of cells, called juxtaglomerular cells, sense the blood pressure. When your blood pressure drops, so does the amount of filtered sodium. This information is picked up by the macula densa cells and they relay it to the juxtaglomerular cells, which release an enzyme called renin. Renin gets converted into angiotensin II, which causes blood vessels to contract and increase your blood pressure.

Angiotension II also stimulates the secretion of aldosterone, a hormone that stimulates more sodium reabsorption, which increases blood volume and, in turn, blood pressure so that vital organs continue to receive the necessary blood, oxygen and nutrients.

Your blood pressure will vary according to exercise, emotional or mental stress and caffeine. But you will have a baseline, hopefully within normal range of 120/80mmHg. There might be fluctuations depending on what you're doing but your kidneys should be able to regulate them and return your blood pressure to its baseline.

The same system can also work in reverse to reduce your blood pressure (by getting you to pass more urine) should it rise for any reason – drinking a cup of coffee, for example.

SMALLER KIDNEYS, BIGGER DEMANDS

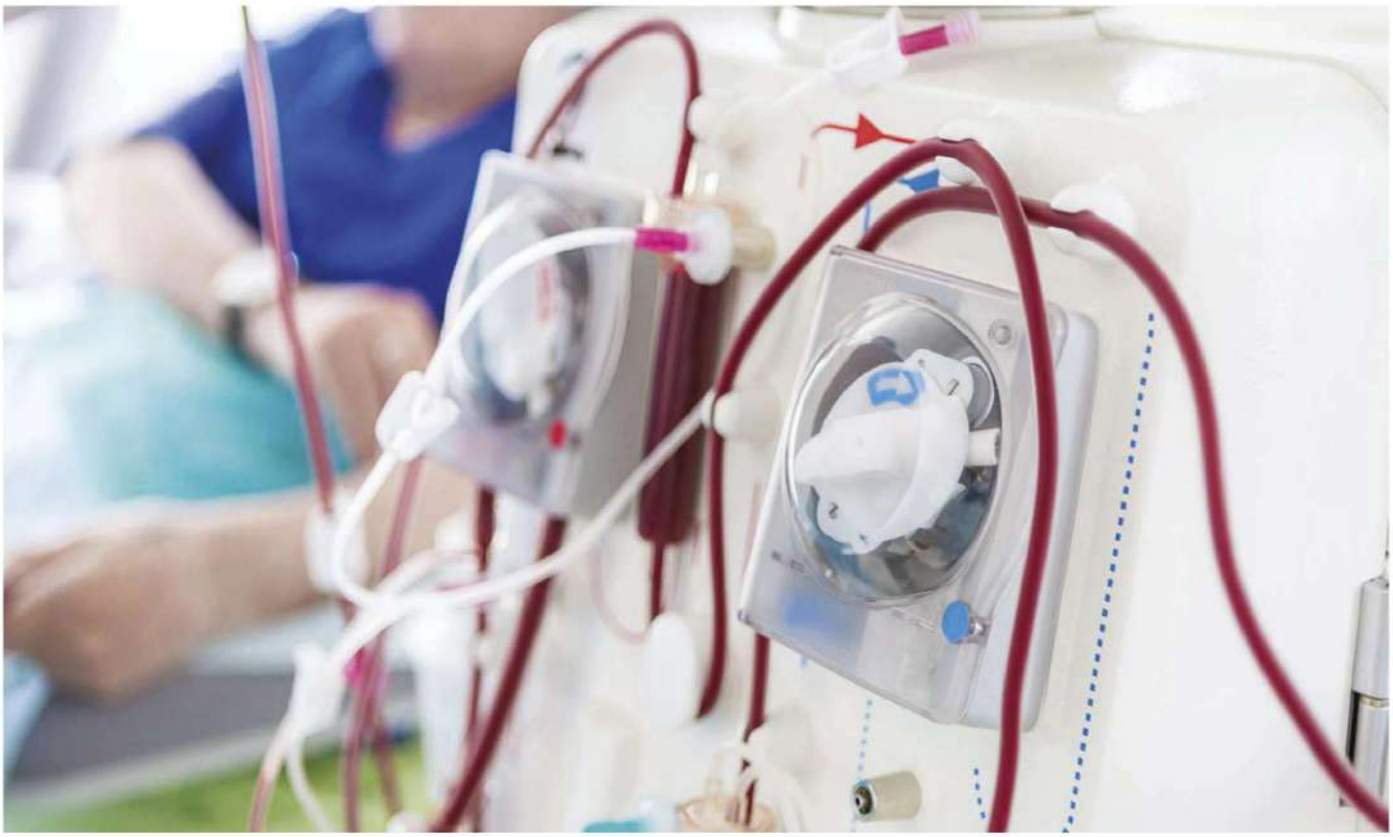
Women generally have smaller kidneys with fewer nephrons than men. The rate of filtration, known as the glomerular filtration rate (GFR), a key marker of renal health, is higher in men than women. Data suggest that GFR declines after 35 years of age and the decline is faster in women. If the decline is persistent then chronic kidney disease is likely.

Women's kidneys also face remarkable demands during pregnancy and will grow by around 30 per cent in order to cope with the increased workload a developing foetus places on them. The mother's GFR can double in the process.

Blood pressure drops approximately 10mmHg by the second trimester despite a 20 per cent gain in circulating volume caused by hormones released during pregnancy that activate the renin-angiostensin-aldosterone system. A rise in aldosterone results in an increase of sodium in the blood, which normally would be concerning as it would cause potassium to drop. In pregnant women, however, there is a parallel rise in progesterone, which prevents that from happening.

TIPPING THE BALANCE

Over the course of a normal day your kidneys continue to work hard to maintain a balance of ions, water and excreting waste.



Dialysis machines are required by people whose kidneys are not able to adequately filter their blood

Stress, be it physical or mental, contributes to increased blood pressure, which your kidneys work to bring back to its normal baseline through the renin-angiotension-aldosterone system. It's only when blood pressure consistently remains above the normal level that there's a risk of damage to vital organs, such as your heart and the kidneys themselves.

During exercise the amount of blood going to your kidneys is reduced as it's directed elsewhere, to the working muscles, so effective renal plasma flow is reduced. Despite this, the level of filtration can double with maximal exercise, preserving the transfer of substances through the glomerulus. Tubular processes and excretion rates are also modified by exercise.

After exercising your kidneys might be 'leakier' than usual, and let through larger molecules that might not pass through when you're at rest. Proper hydration helps preserve the glomerular filtration rate, while an anti-diuretic effect is observed during intense exercise.

It's not just about making urine, though. Your kidneys perform many complex functions that keep the rest of your body in balance. They control the production of red blood cells, make vitamins that control growth and regulate the levels of nutrients such as calcium and potassium.

Healthy kidneys produce a hormone called erythropoietin or EPO when blood oxygen levels are low. It acts in bone marrow to stimulate the production of mature red blood cells, to maintain healthy oxygen levels in your tissues. EPO prompts bone marrow to make red blood cells, which are then released into the bloodstream. If your kidneys are damaged, they don't make enough EPO, resulting in a condition called anaemia, which leaves you feeling tired and weak because you're lacking the necessary amount of red blood cells to carry oxygen to your muscles.

Your kidneys also convert Vitamin D into a form that your body can use. Activated vitamin D stimulates the uptake of calcium from food (important for the maintenance of healthy bones) and also helps to regulate your immune system. But most of the vitamin D in your blood is inactive until its modified and activated by your kidneys.

If your kidneys aren't working correctly, waste

You can live quite safely with just one kidney, but you have to take very good care of it... because you don't have a back-up

products and excess fluid build up, and you're your sodium, potassium, phosphate and calcium levels aren't regulated correctly. When these substances gather together, this causes the symptoms of kidney disease, which include high blood pressure, lethargy, fluid retention and can also be life threatening.

Kidney damage can occur for a number of reasons – diabetes, high blood pressure, infections and a group of diseases that affect the glomerulus. Kidneys need an adequate supply of blood, so if something disrupts this, they will be prevented from working efficiently. You also have to take care with medications as some are 'nephrotoxic' – toxic to kidneys.

CARE AND SHARE

Generally speaking, most people have two kidneys. But, for various reasons, some people only have one. You can live quite safely with just one kidney, but you have to take very good care of it (by eating a healthy diet, exercising regularly and drinking plenty of fluids) because if you've only got one, you don't have a back-up. It also means diligently staying away from nephrotoxic medications.

Why might you have only one kidney? You may have been born with only one functioning kidney or disease has led to one of your kidneys failing. You may even have decided to donate a healthy kidney to someone suffering kidney failure – an act of considerable kindness that enables the recipient to live a normal life, instead of having to undergo dialysis up to three times a week.

The best way to keep your kidneys healthy is simply to look after yourself. That means eating well, drinking plenty of water and exercising regularly. Guard against developing diabetes because this can have an impact on kidney function. Diabetes and high blood pressure are the two leading causes of kidney failure – if you have either, discuss ways you can address the issue with your doctor. It might require lifestyle changes and weight loss.

If you're on long-term medications, make sure you check to see if they have any impact on your kidneys and, if they do, then make sure your GP keeps a regular check on the function of your renal system through simple tests. **SF**

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RENAL STONES

Various factors contribute to stones forming in your kidneys but they all lead to the same end result... pain

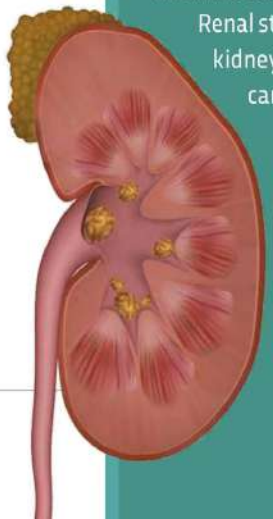
Renal stones are extremely common – 15 per cent of the global population suffer from them at any one time. They are solid pieces of material that develop in the kidneys, causing mild to extreme pain. The pain can get so severe that you may even vomit and need to visit A&E.

There are four types of stones: calcium stones (the most common) are usually formed from calcium oxalate, often due to dietary factors, metabolic disorders or intestinal bypass surgery; struvite stones form quickly, sometimes with no symptoms, and are linked with infections of the urinary tract; uric acid stones are caused by high-protein diets and drinking too little fluid; and cystine stones form in people with a genetic disorder that causes them to excrete excessive amounts of amino acids.

Renal stones form in the kidneys and in some cases can pass through your body in the urine stream without a problem. But a large stone of 5mm or more can cause a blockage, hence the severe pain that will radiate from your flank to your groin on the side that the stone sits. They may also make it painful for you to urinate and there might be blood present in the urine you pass.

So what causes them? Risk factors include obesity, certain foods, medication, calcium supplements and poor fluid intake. A doctor will be able to identify a stone through the symptoms described above, but they'll also look for it using a CT scan to see its location and size.

Depending on the size of the stone, it might be a case of pain relief with non-steroidal drugs or opiates and then waiting to see if it passes. If there are multiple stones, then you may need a treatment called shock wave lithotripsy, which breaks the stones into small pieces to them to pass. Larger stones may require surgery to be removed. For people who suffer from stones, avoiding the risk factors can help prevention, such as drinking plenty of fluids but avoiding soft drinks that contain phosphoric acid.



ABOVE: Kidney stones that have been removed from patients

LEFT: Blockages due to stones can lead to pyelonephritis, in which puss builds up in or around the kidney

BREAKTHROUGHS

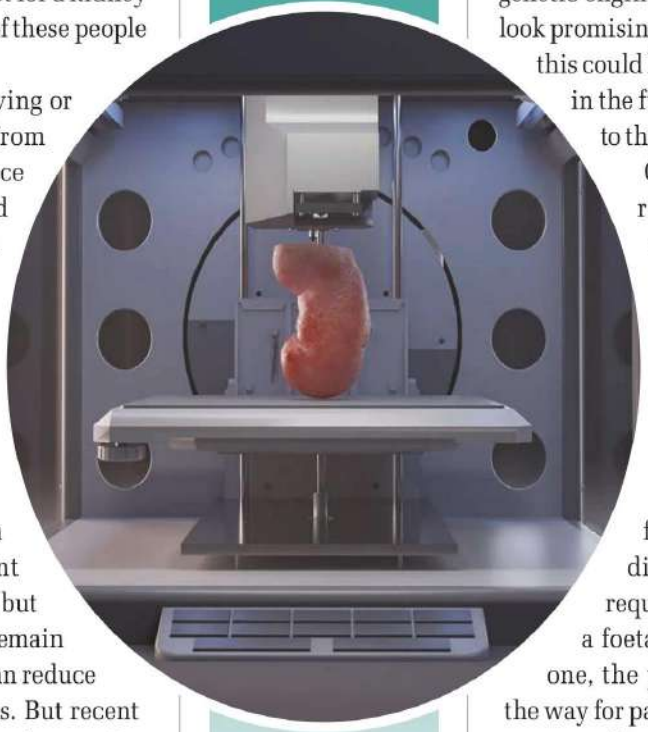
Next-level kidney care

Lack of donors, dialysis or a lifetime of immunosuppressant drugs – the latest medical advances are getting closer to solving the dilemmas faced by people in need of a kidney transplant

More than 5,000 people are currently on the NHS waiting list for a kidney transplant. Sadly 250 of these people die each year.

Kidney donors can either be living or recently deceased, but organs from living donors offer a better chance of success. Outcomes are still good with the latter, however, and that's why the opt-out scheme for organ donation will make a significant difference for those people awaiting a kidney donor.

Nevertheless, there is still concern that we need other options to meet the demand for organs and reduce the risk of rejection or failure. Immunosuppressant medication can reduce this risk, but recipients of donor organs have to remain on the medication for life, and it can reduce their ability to fight off infections. But recent breakthroughs mean we could soon be entering on a new era of kidney care, with a wide range of possible treatments from a wearable artificial kidney to more effective and targeted drugs to make transplantation easier.



3D printed kidneys could be one possible solution to the currently unmet need for donor organs

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3D PRINTING, PIGS AND GENETIC ENGINEERING

One project that could transform kidney patient care is investigating the possibility of making personalised kidneys using a 3D printer and the patient's own tissue. It could significantly reduce, if not eliminate, the risk of rejection.

Another idea being explored is cross-species transplantation, so-called xenotransplantation, as researchers have found that human and porcine kidneys are remarkably similar. But despite large advances, immunological reactions leading to rejection remain the limiting factor. There is hope, however, as preclinical trials involving genetic engineering and embryonic xenografts look promising. Should it prove to be successful, this could lead to mass production of kidneys in the future, presenting a viable solution to the growing problem of renal failure.

One of the most anticipated and remarkable advancements in organ transplantation research surrounds the use of stem cells. In trials, stem cells from the kidney donor's blood are introduced to a recipient's immune system to create an environment that won't reject the new kidney.

Pluripotent stem cells derived from adult humans have also been directed to form the major cell types required for a foetal kidney. Although a foetal kidney is different to an adult one, the potential is clear. It would pave the way for patient-specific tissue, minimising, or even eliminating entirely, the need for immunosuppressant medication.

One such study has taken place in Chicago at the Comprehensive Transplant Center, Northwestern Memorial Hospital. It found that an injection of stem cells given alongside a kidney transplant could remove the need for a lifetime of immunosuppressants. Five of the eight patients involved were able to have their medication reduced within one year. Additionally, there was no evidence that the donors' transplanted immune cells had attacked the recipients' healthy tissue.

This is only early-stage research, but the results are promising, with life-changing implications for the future of organ transplants, particularly in those cases where the donor and recipient are not a perfect match. **SF**

by **DR SALEYHA AHSAN** (@SaleyhaAhsan)
Dr Ahsan is a practising A&E doctor and a presenter on BBC Two's Trust Me I'm a Doctor.

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Reproductive SYSTEM

While the hormones and organs of your reproductive system have a range of effects on your own body, they can only perform their primary task in conjunction with a partner of the opposite sex. But despite the collaboration required to conceive an offspring, the scales of the biological factors involved are not balanced: women produce one egg a month; men produce around 1,500 sperm every second. Which goes some way towards explaining why a safe, reliable and reversible male contraceptive pill has yet to be found

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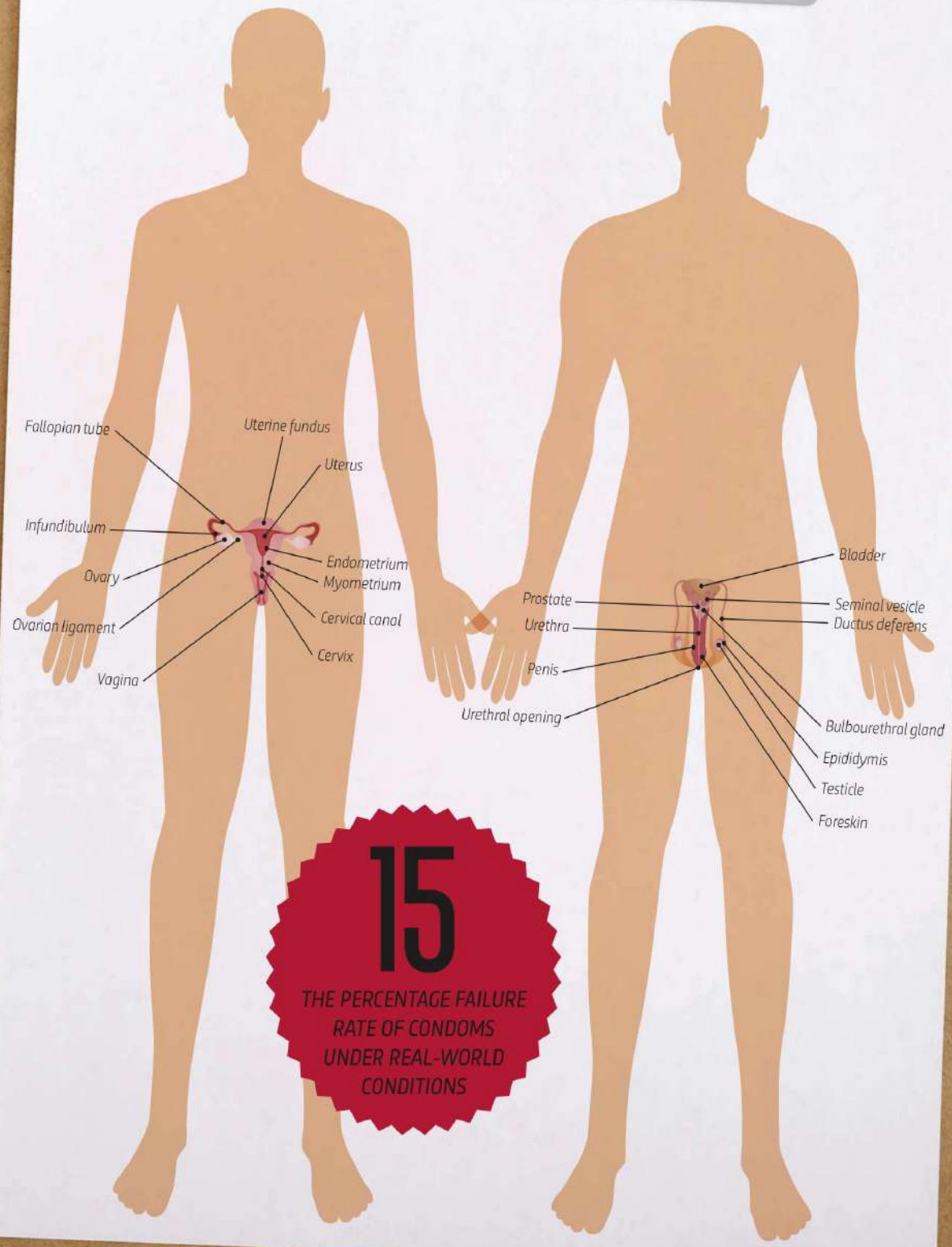

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THE PERCENTAGE FAILURE RATE OF CONDOMS UNDER REAL-WORLD CONDITIONS


Do not touch,
may cause leakage

SPERM STOPPERS

THE SEARCH FOR A MALE CONTRACEPTIVE PILL

For over half a century, women have been able to take control of their reproductive systems to prevent pregnancies. But many men want the same ability. So how come there's no male pill?

words by DR KAT ARNEY

More than 50 years ago, in 1960, the first female hormonal contraceptive pill, Enovid, was approved by the US Food and Drug Administration (FDA), with the UK following in 1961. Just five years later, millions of the pills were being swallowed every day as women around the world took control of their reproductive choices and health, creating a seismic change in society.

Today, women have a wide range of reliable, reversible options for controlling their fertility, including intrauterine devices (IUDs), patches, jabs and implants. Men have just two: condoms, which have a 15 per cent failure rate and are disliked by many couples, and vasectomy – cutting the tubes that shuttle sperm from the testes to the penis. So why isn't there a male pill?

The history of the male contraceptive pill has been a lot more turbulent than the female pill. Its origins date back to the 1950s, when US biologist Dr Gregory Pincus, one of the co-inventors of the female pill, found that doses of a synthetic version of the male sex hormone testosterone could switch off sperm production in the same way that the female hormones in the pill shut down ovulation.

"The physiology and science behind the male hormonal contraceptive pill is analogous to the female pill," says Prof Stephanie Page, an expert in male reproductive biology at the University of Washington in Seattle. "Giving men an external source of testosterone blocks their production of the hormone in organs like the testes. They still have plenty of it in their blood, so it doesn't affect the rest of their body, but developing sperm need 100 to 1,000 times as much testosterone for their final maturation and there just isn't enough in the testes for them to finish developing."

BBC RADIO 1

Find out what the future might hold in store for male and female contraception. *bbc.in/2YeoVHh*

NO SWIMMING... OR WRIGGLING

At the University of Minnesota, chemistry professor Dr Gunda Georg is taking an alternative approach. She and her colleagues are investigating a chemical called ouabain – a potent toxin produced by plants, which was originally used by east African tribes to coat the tips of their hunting arrows.

Ouabain blocks molecules called sodium potassium ion transporters, which normally shuttle salts in and out of cells. Curiously, ➤

GETTY IMAGES

one particular component – the alpha 4 subunit – is only found in transporters in sperm cells, and nowhere else in the body.

"When we removed the gene encoding the alpha 4 subunit in male mice, we found that they were quite normal in all respects except that they were infertile," Dr Georg says. "The animals even made normal sperm, but they couldn't swim up the fallopian tube to get to the egg or do the final wriggling movement that leads to fertilisation. This suggested that if we could develop a drug that selectively blocks alpha 4, this would be a promising approach for male contraception."

Dr Georg and her team began looking for ways to modify the chemical structure of ouabain so it would only hit alpha 4. Then once they'd tweaked the molecule, they tested it in rats to see if it would work. Amazingly, they hit the jackpot first time.

"It turned out that we'd found a very potent compound that had high activity even at low doses and could be given orally – it was pretty exciting for us to get it right on the first attempt!" she laughs.

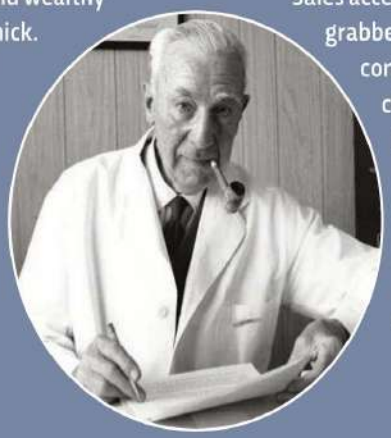
"The science behind the male pill is analogous to the female pill"

At the moment the researchers have only tested the drug in animals, but it seems to reduce sperm mobility by around 50 to 60 per cent. However, there are still a few issues that Dr Georg and her colleagues need to address before they can move forward into human trials. For a start, they want to develop an even more potent version of the drug which would still be effective at smaller doses. The next step is to carry out long-term animal mating studies to see how well it works to prevent pregnancies and whether there are any hidden side effects. More importantly, they also need to make sure that the drug is reversible and doesn't cause any birth defects or other health concerns in the subsequent offspring.

A BRIEF HISTORY OF THE PILL

The story of the female contraceptive pill starts in the 1950s, when US researcher Dr Gregory Pincus (right) started searching for chemicals that interfere with fertility in animals. He figured out that giving female animals doses of the sex hormone progesterone would shut down ovulation, preventing eggs from being released.

Pincus teamed up with gynaecologist Dr John Rock (below), who was already testing chemical contraception in women, and they secured funding from women's rights activist, biologist and wealthy heiress Katherine McCormick. At the same time, Dr Carl Djerassi, a chemist working in Mexico, was working out how to create artificial hormones from inedible yams. Eventually he managed to make norethindrone – a synthetic version of progesterone.



Enovid – a combination of artificial oestrogen and progesterone – first went into clinical trials in Massachusetts in 1954, with larger-scale studies taking place in Puerto Rico in 1956. Initially approved by the FDA for menstrual disorders, it was finally given the green light as a contraceptive in 1961.

Sales accelerated rapidly as women grabbed the chance to take control of their reproductive choices and health. Since then, millions of women all over the world have taken hormonal contraception, and there are many versions on sale. The pill is extremely effective at preventing pregnancy, with an almost 100 per cent success rate as long as it's taken correctly, and it can also help with irregular or painful periods.

The success of the pill is tempered by growing concerns about possible side effects that may not have been flagged up by the early clinical trials. By 2010, there were more than a thousand pending lawsuits claiming that various pills could cause blood clots, heart attacks and strokes. Large studies have shown that it can increase the chance of breast and cervical cancers (although it reduces the likelihood of developing womb or ovarian tumours) and some studies have suggested that hormonal contraception can affect mental well-being and may even increase the risk of suicide.

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1. Enovid (called Enavid in the UK) was the first hormonal female contraceptive pill. Modern pills contain much lower doses of hormones than earlier versions

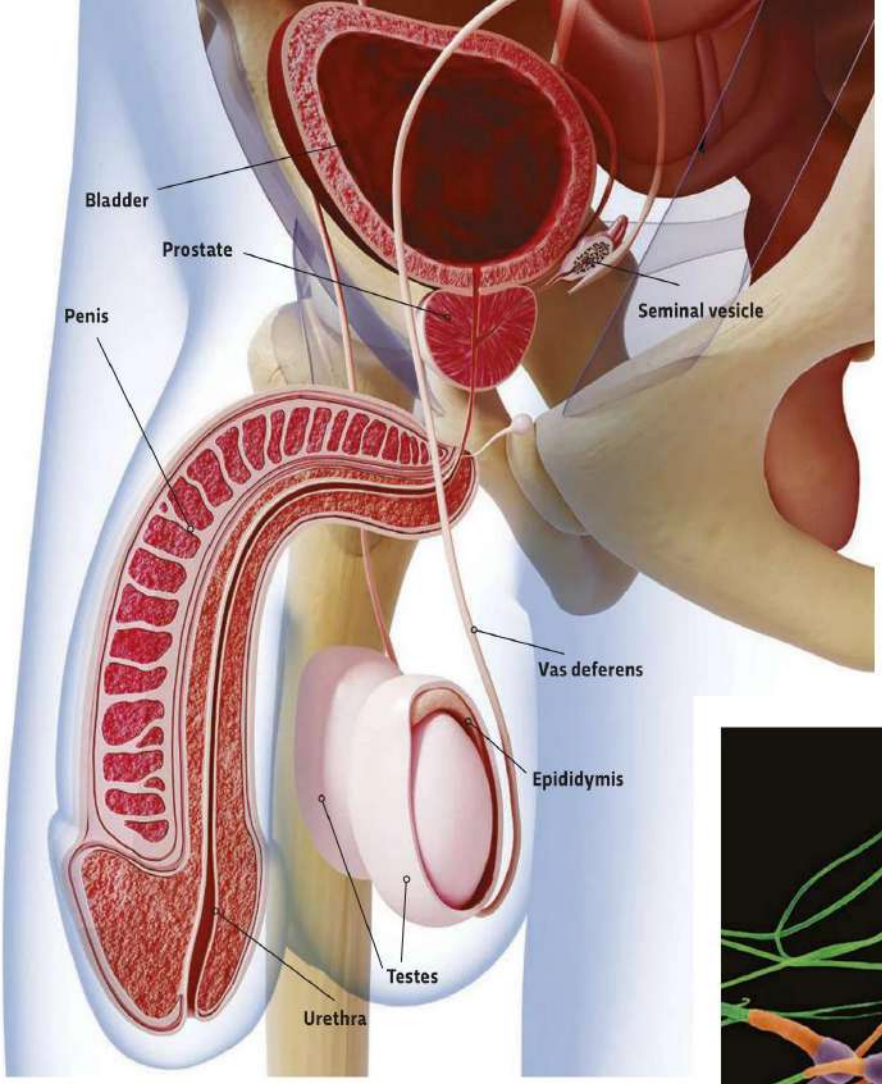
2. Attempts at making a male contraceptive pill have been underway for years – this prototype, from Dutch pharmaceutical company Organon, dates back to 2001

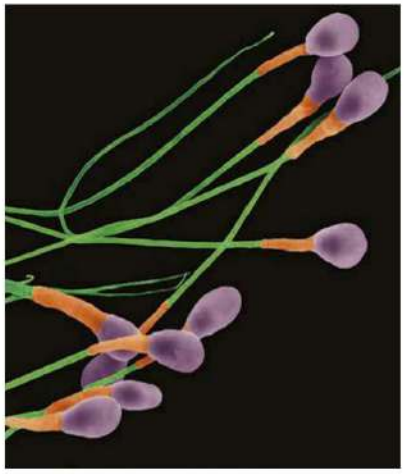
3. A social worker discusses the contraceptive pill with a client in 1970

4. Dr Gregory Pincus worked on developing the first female contraceptive pill and also realised that male hormones could switch off sperm production in men

5. Crystals of testosterone, the male sex hormone

ALAMY X2, SHUTTERSTOCK, GETTY X3, SCIENCE PHOTO LIBRARY





RIGHT: Male pills tend to either prevent sperm (seen here under a scanning electron micrograph and coloured) from developing in the testes, or somehow impede their movement so they can't reach the egg

Another option is to interfere with the 'plumbing' of the testes, so that sperm can't be pumped out during ejaculation. To investigate this, Prof Sab Ventura and his team at Monash University in Australia been given a $150,000 grant from the Male Contraception Initiative – a non-profit organisation dedicated to promoting public awareness of male contraceptives.

"Before ejaculation, sperm is moved from the testes to the end of the penis along a tube called the vas deferens," Prof Ventura says. "We're trying to disrupt the nerve signals that tell the muscles around the vas deferens to contract, so that the man still has a pleasurable orgasm but no sperm come out."

In order to do this, Prof Ventura is investigating a combination of drugs that would completely block both of the types of nerve signals received by the vas deferens, which are sent through neurotransmitter chemicals called ATP and noradrenaline.

"Our approach is non-hormonal so it won't have any of the unacceptable side effects that have been seen in the trials of hormone pills," he says. "It doesn't affect sperm development, just the plumbing, and we can show that the sperm are still fine and can be used to fertilise eggs in vitro. So we think it's highly likely to be reversible and that there's a low chance of causing deformities in babies further down the track."

SUPPLY AND DEMAND

Despite the progress in research, there's no chance of a male pill taking off if there's no market for it. In 2011, Cambridge-based social scientist Dr Susan Walker surveyed attitudes towards the male pill in a group of 54 men and 134 women, all of whom were already using some form of contraception. Just under half the respondents said they would be happy to take a male pill although worries about health risks and effects on long-term fertility also came up. But more than 40 per cent worried about forgetting to take it, with women more concerned about this than men. Larger studies across several continents have come to broadly similar conclusions, showing that men have a preference for contraceptive pills rather than jabs or other delivery methods.

Even though many men say they would happily take the pill, there are still significant regulatory and financial hurdles to be overcome. Because there are no male contraceptives currently on

"Even though many men say they would happily take the pill, there are still significant hurdles to be overcome"

the market, regulatory bodies like the FDA are unsure as to how to measure the effectiveness and acceptability of a male contraceptive drug. And although there's a large potential market for a male pill, pharmaceutical companies are unwilling to make the investment required to push a candidate pill through large-scale clinical trials in order to get approval.

According to Dr Walker, this all comes down to the difference in risk between male and female contraception. "A person who takes the female pill is the one who will be affected physically and biologically by an unplanned pregnancy. A man is not directly and physically affected by pregnancy – although he may be socially, psychologically and financially affected – so we're working in a different framework for risk," she says, pointing out that childbirth still carries a small chance of serious health problems and even death.

"We have to judge whether the health risks of any type of contraception outweigh risks of pregnancy based on the health of that individual and any other conditions they might have. That nuanced calculation of risk hasn't had a chance to take place around the male pill, because we're not at that stage yet," she adds.

Any contraceptive pill can't prevent sexually transmitted diseases, though so condoms will still be a necessity in encounters where that is a risk. But ultimately, the search for the male pill is all about empowering men who want to play their part in preventing pregnancy and providing more options, particularly for couples where the woman is unable to use other forms of contraception.

"We think the time is right to move this forward because men are more open to rethinking social responsibility and what they want out of a relationship, and even protecting their own fertility," says Prof Page. "We're underestimating that men want to be more involved – it's just they have such crummy choices. This is all about having more options, so what will really drive it is demand from men to have more control and share the responsibility for preventing unplanned pregnancies." **SF**

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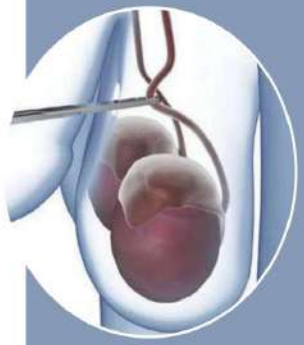
by **DR KAT ARNEY** *(@Kat_Arney) is an award-winning science writer and author of How to Code a Human.*

POPPING PILLS AND PLUGGING THE PLUMBING

Here are some alternative ideas for male contraception coming down the pipeline...

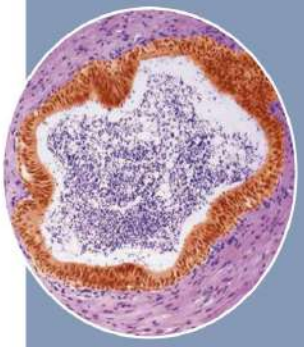
1 HERBAL REMEDIES

Gendarussa (also known as gandarusa) is a compound from the Chinese *Justicia gendarussa* plant, which is thought to disrupt fertilisation. It's currently being tested in small trials in Indonesia to see whether it is safe and effective. Another potential contraceptive is pristimerin, which comes from an ancient medicinal herb known as the thunder god vine.



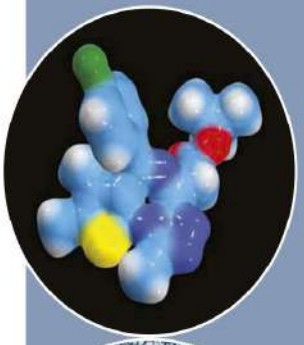
2 VAS-OCCLUSION

Vas-occlusion techniques physically block sperm from moving along the vas deferens – the tube that transports them from the testes to the penis – by using injectable polymers that can be reversed at a later date by injecting a 'dissolver' chemical or using ultrasound. The best-known of these techniques is called Vasalgel, which has been successfully tested in monkeys and, if funding can be secured, is expected to move forward into clinical trials soon.



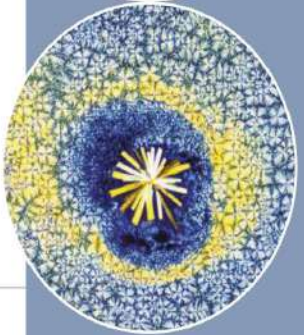
3 CLEAN SHEETS PILL

This is an experimental drug that paralyses the muscles that squeeze sperm out of the vas deferens, resulting in a 'dry' orgasm. It's being developed by Nnaemeka Amobi, formerly a researcher at King's College London, but has stalled due to lack of funding.



4 JQ1

JQ1 was initially developed as a drug that specifically targets a faulty molecule that drives a rare type of cancer called NUT midline carcinoma. But it also stops sperm from developing properly by blocking a molecule that is essential for packaging up DNA inside sperm.



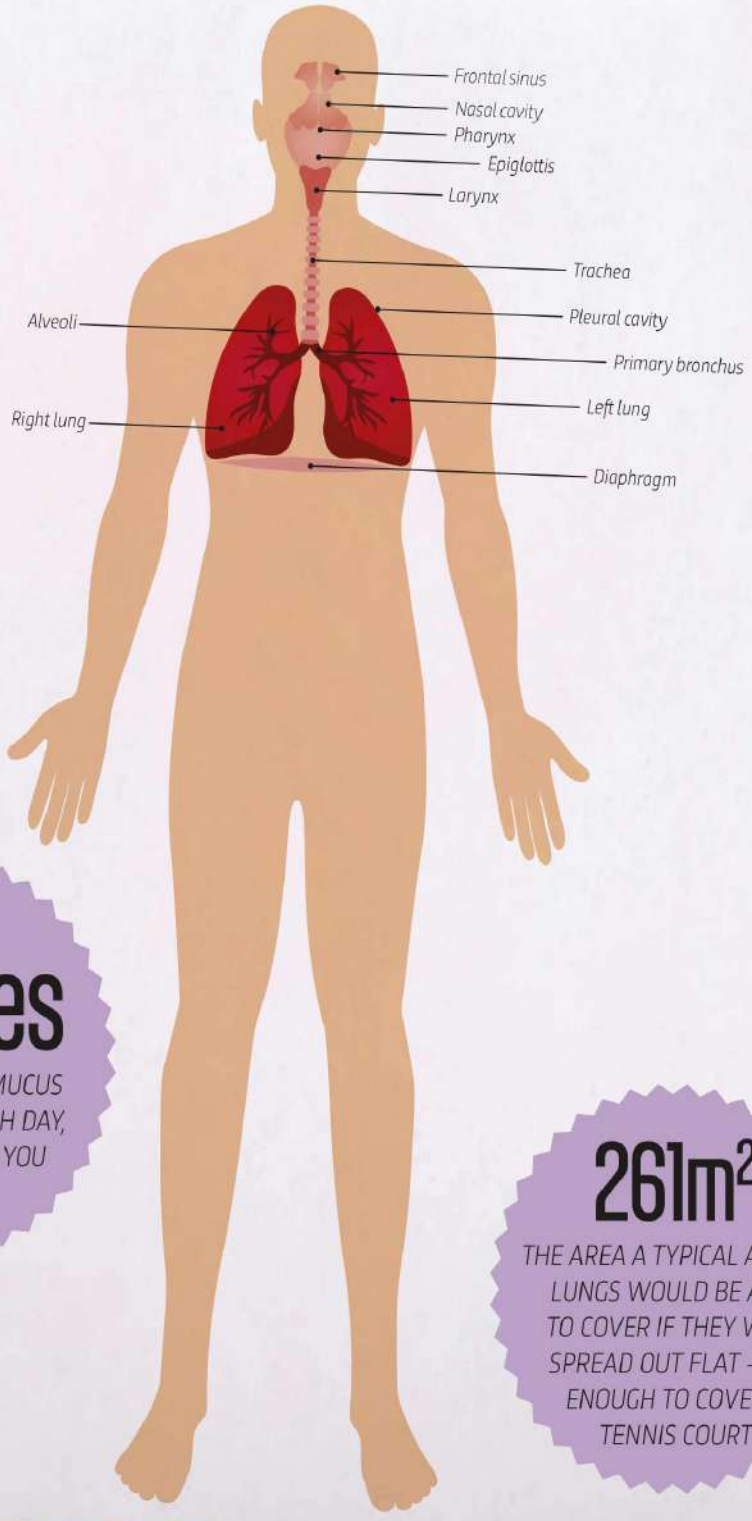
5 RETINOIC ACID

Sperm production depends on a steady supply of retinoic acid, a chemical produced when vitamin A is broken down in the body. Controlling how retinoic acid is produced and used in the testes, perhaps by blocking the enzymes that break down vitamin A, could lead to new ideas for male contraceptives.

Respiratory SYSTEM

Your respiratory system is how the oxygen in the air gets into your blood. It's also how you get rid of the carbon dioxide produced by your body converting food into the energy it needs to keep all your organs functioning. Given the job it has to do, your respiratory system is remarkably robust. But it's by no means invulnerable. We know the sort of damage smoking can cause over the long term but there's another equally potent threat facing our lungs: air pollution

GETTY IMAGES X2, VECTORSTOCK



1.5 litres

THE AMOUNT OF MUCUS YOU PRODUCE EACH DAY, MOST OF WHICH YOU SWALLOW

261m²

THE AREA A TYPICAL ADULT'S LUNGS WOULD BE ABLE TO COVER IF THEY WERE SPREAD OUT FLAT – IT'S ENOUGH TO COVER A TENNIS COURT

EVERY BREATH YOU TAKE...

...sees you draw a small part of the outside world into the deepest recesses of your body. Which is why your respiratory system has to work so hard – it not only has to absorb all the oxygen it needs to keep you alive but also filter out all the filth that's floating around in the air in our cities. Your lungs are a purification and protection system all rolled into one, and their job is getting harder

words by TOM IRELAND

Roughly 10 seconds after a baby is born, it takes its first breath. Its lungs inflate and the fluid that filled them while the baby was in the womb begins to drain away. Now these remarkable organs begin their job of getting oxygen into the baby's bloodstream and expelling carbon dioxide, and will do this unceasingly for the rest of its life.

In, out, in, out... your lungs inflate and deflate up to 20 times a minute, tens of thousands of times a day. Just five or six minutes without oxygen is usually deadly: cells begin to produce toxins and malfunction almost immediately, and organs such as the brain and heart start to fail.

Yet you rarely think about breathing – you don't have to because the process is controlled unconsciously by your brain. Although you can regulate your breathing when you need to – for example if you're about to dive underwater – it would be annoying to have to think about it every minute of every day.

Instead, your 'respiratory centre', in the base of your brain, largely keeps you breathing on autopilot. A complex hormonal feedback system, involving receptors around your body measuring oxygen and carbon dioxide levels, ensures your breathing rate quickly rises or falls to match the needs of your body.

Each breath is akin to a pair of bellows in your chest being opened and closed, drawing air in and out of your body. Muscles around your rib cage and below your lungs contract, making the chest cavity larger and causing air to rush in and fill it. When these muscles relax, your ribs fall back into place, pushing air out.

Without the evolution of this system, it's unlikely that animals of our size and bigger would exist. Terrestrial animals without lungs, such as insects or salamanders, get oxygen into their systems through holes in their bodies or by absorbing it through their skin, which is very efficient but limits how big they can grow. (Although in the ancient past, when there was more oxygen in the air, lungless animals such as insects, snails and worms grew to huge sizes.)

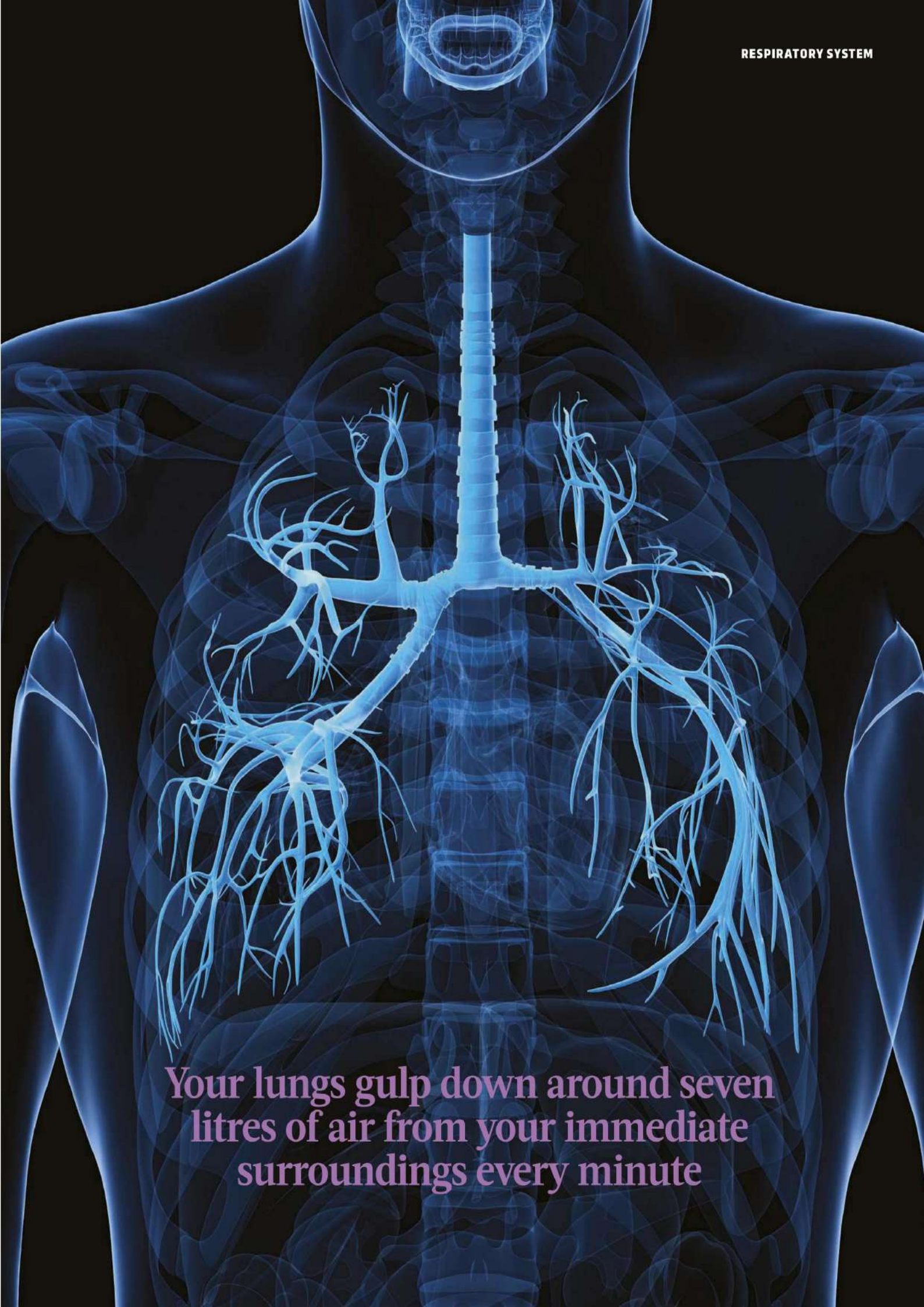
GAS EXCHANGE

The classic school textbook fact – that all the tissue in your lungs flattened out would cover a tennis court – is absolutely true. The structure of the lungs has evolved as a way to pack as much gas exchange surface area as possible into a small space.

When air is sucked into your lungs, the nose filters, warms and moistens it before it passes down your windpipe. The windpipe branches into smaller and smaller tubes known as bronchioles, which are lined with muscle to allow them to widen or constrict. The bronchioles continue to branch into finer tubes that lead into microscopic air sacs. The average adult has around 300 million of these tiny sacs, known as alveoli.

The alveoli have very thin walls and are entwined with equally tiny blood vessels ➤

GETTY IMAGES



Your lungs gulp down around seven litres of air from your immediate surroundings every minute

known as micro-capillaries. As oxygen-rich air is sucked into the alveoli, oxygen diffuses across these walls into the oxygen-depleted blood passing by. At the same time, carbon dioxide diffuses in the opposite direction, from the blood into the alveoli, ready to be exhaled. Once blood has passed through your lungs and exchanged carbon dioxide for oxygen, it flows to the heart, and is pumped to the rest of your body.

OUTSIDE IN

It's easy to think of the lungs just as breathing organs, but they have another vital job to do. They are the primary interface between the inside of your body and the outside world. Your lungs gulp down around seven litres of air from your immediate surroundings every minute. So the respiratory system is the front line of your body's defence against invaders, with your nose sampling the air you breathe for signs of danger (and food).

The air around you is rarely only composed of the nitrogen, oxygen and other gases that make up Earth's atmosphere. It often contains smoke, dust, bacteria, pollen and viruses – and as you suck this cocktail into your body, your lungs not only have to stop it getting into your blood but also get rid of it.

To achieve this your lungs rely on an amazing self-cleaning system that pairs thick mucus with microscopic hair-like structures, called cilia, that line the cells of the airways. The sticky mucus catches the particles that you inhale while the cilia vibrate up to 600 times every minute to pulse the mucus and trapped particles up and out of the lungs.

"It's thought that we inhale over a million bacterial particles a day, yet we rarely get lung infections," says James Chalmers, a professor of respiratory research at the University of Dundee. "The lungs are great at getting rid of things we've inhaled. Think of smoking – that's a lot of toxins, but it can take 20 years of smoking 20 cigarettes a day before the system is overwhelmed."

Without you noticing, some of this bacteria and particle-filled mucus rises up your throat, where it's swallowed and then destroyed by your stomach acid. Mucus reaching your nostrils gets dried out quicker than the stuff that's deeper in your respiratory system, and as it dries forms what are commonly referred to as 'bogeys'.

"You produce 1.5 litres of mucus a day to wash particles out of your lungs and most of it is reabsorbed by your lungs," says Prof Chalmers. "Patients are often either impressed or revolted by the fact that they swallow about a can of Coke's worth of mucus every day. You just don't notice because it's happening all the time."

"It's thought that we inhale over a million bacterial particles a day..."

DIRTY AIR

The respiratory system's role on the front line of your body's defences is what makes the lungs so susceptible to disease. Common disorders like asthma are a result of the lungs having to deal with large quantities of allergens, such as pollen, every day. But why do some people suffer from asthma and others lung disorders, while others don't?

Professor Louise Wain, British Lung Foundation chair in respiratory research at the University of Leicester, studies how people's genes can make them more susceptible to lung diseases. "The accepted view is that lung diseases, such as asthma are triggered by environmental pollutants, but certain people will have a genetic predisposition that makes them more at risk. People's genes can also affect how effective treatments will be."

On top of the challenges dust, pollen, bacteria and viruses pose to your lungs, there's the growing threat of toxic air pollution. This deadly mix of sooty particles and poisonous gases often reaches dangerous and illegal concentrations in urban areas, where exhaust fumes from traffic and industrial emissions linger at ground level.

Poor air quality causes a range of health problems, from short-term effects such as sneezing, coughing, eye irritation, headaches and dizziness, to more serious reactions like asthma

Skyscrapers poke through the morning smog that blankets the Chinese city of Shanghai – the most densely populated city in the world and an urban centre renowned for its poor air quality

BBC RADIO 4

Listen to *Costing The Earth* to find out what you can do to improve the quality of the air you breathe *bbc.in/32XaqGt*

ALAMY, GETTY IMAGES

attacks, as well as increasing the likelihood of heart disease, strokes and various cancers.

The particles in air pollution are so fine that they can get into your lungs and cross into your bloodstream. Research has even found some of these particles lodged in the brains of people who live near pollution hotspots. Toxic gases from car exhausts, such as carbon monoxide, nitrogen dioxide and sulphur dioxide, have a direct effect on the respiratory system and long-term exposure is associated with shortened life expectancy. Globally, poor air quality is thought to cause an estimated 4 million premature deaths per year and 90 per cent of us live in areas where air pollution exceeds World Health Organisation guidelines. The UK is regularly in breach of its own laws on what constitutes safe air to breathe.

VENTILATION, EXHAUST AND DEFENCE

Aside from smoking, air pollution is possibly the most serious threat your lungs and respiratory system face – but you can't see or smell the danger. In 2018, an inquest found that unlawful levels of air pollution near the South Circular Road in Lewisham, south east London, had caused the death of Ella Kissi-Debrah. Ella, who was just nine years old, grew up by the busy road and died of a severe asthma attack after having been repeatedly hospitalised with seizures and breathing problems.

Your lungs are your ventilation, exhaust and defence systems all rolled into one, and unless they go wrong in some way, they never stop working. They already perform a miraculous feat by filtering tens of thousands of litres of air every day to provide the oxygen needed to keep you alive, even while you're asleep. The damage caused by smoking cigarettes and the air pollution are a warning to us all not to take the respiratory system for granted.

"You don't think about breathing until something goes wrong," says Prof Wain. "Imagine having to think about every breath because each one is a struggle. That's what having a lung disease is like." **SF**

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by **TOM IRELAND** (@Tom_J_Ireland)
Tom is a science writer and editor of ***The Biologist****, the Royal Society of Biologist's magazine.*

DEEP BREATHS

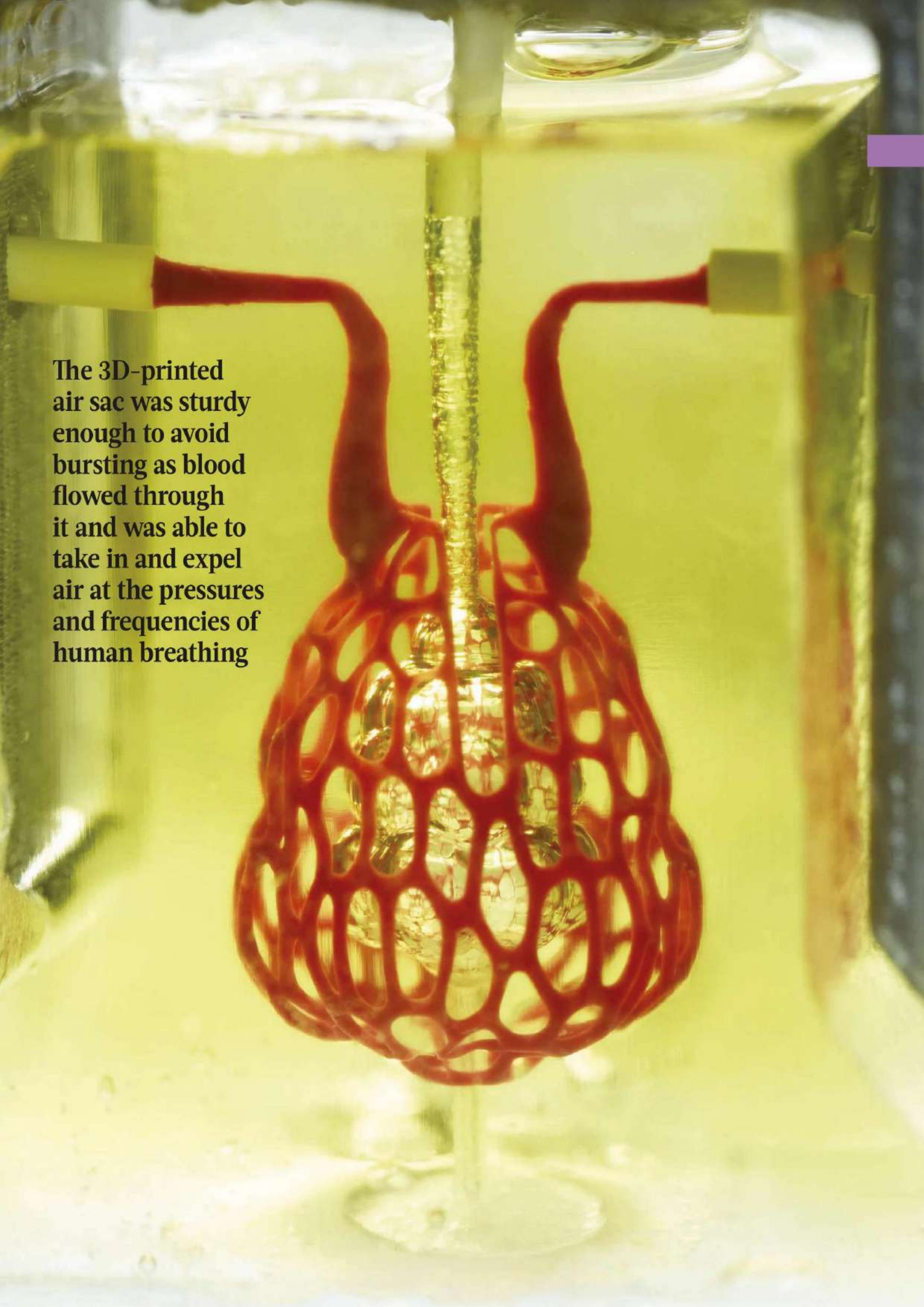
"Now, if you'll just blow into this for me..." How doctors check the size, strength and health of your lungs

The standard way to measure how well someone's lungs are functioning is known as spirometry. A patient is asked to take a very deep breath and blow into a spirometer as fast as they can until no more air comes out. The device measures both how much air they can force out in one second (forced expiratory volume in one second, or FEV1) and the total amount of air they can push out of their lungs (expiratory forced vital capacity, or FVC). This tells doctors about the strength and capacity of the patient's lungs, and can help diagnose lung problems such as asthma, chronic obstructive pulmonary disease (COPD) or cystic fibrosis.

Further tests can be conducted to see how well gases are absorbed by the lungs, comparing the concentration of gas in the air being inhaled with the air exhaled.

A low-tech but very useful diagnosis tool is simply listening to the lungs with a stethoscope. The doctor can listen for abnormal sounds, or a lack of sound, coming from certain sections of each lung during each breath, which may indicate a blockage, disease or damage in that area.

The right lung has three distinct lobes, while the left has two and is slightly smaller to ensure there is space for the heart behind the ribs.



The 3D-printed air sac was sturdy enough to avoid bursting as blood flowed through it and was able to take in and expel air at the pressures and frequencies of human breathing

BREAKTHROUGHS

Print your own body parts

Synthetic organs suitable for transplant could be ready in as little as two decades

words by JASON GOODYER

The image on the left shows a 3D-printed model of a lung-mimicking air sac complete with airways capable of delivering oxygen to surrounding blood vessels. It was made by a team of researchers in the US by gradually building up layers of hydrogel, a synthetic, jelly-like material that shares many features with human tissue.

The same technique could be used for creating complex, entangled vascular networks that mimic the body's passageways for blood and other vital fluids, potentially opening up a means of bioprinting human organs for transplant, the researchers say.

The work was led by Rice University's Jordan Miller and the University of Washington's Kelly Stevens, along with collaborators from Duke University, Rowan University and Nervous System, a design firm in Somerville, Massachusetts. Dubbed 'Stereolithography Apparatus for Tissue Engineering', or SLATE, Miller and Stevens's technique works by building up layers of a liquid pre-hydrogel solution that become solid when exposed to blue light. It can produce soft, 3D structures made from water-based, biocompatible gels with intricate internal architecture in minutes.

In tests, the 3D-printed air sac was sturdy enough to avoid bursting as blood flowed through it and was able to take in and expel air at the pressures and frequencies of human breathing. It was also found that red blood cells could take up oxygen as they flowed through a network of blood vessels surrounding the air sac – a process similar to the gas exchange that occurs in the lungs.

JORDAN MILLER/RICE UNIVERSITY X2

LEFT: The 3D-printed model of a lung-mimicking air sac

BELOW: Bagrat Grigoryan, a bioengineer at Rice University, oversaw the development of a 3D-printing technique that's capable of building functioning vascular structures

FROM THE LUNGS TO THE LIVER

The researchers are already using the new technique to explore more complex structures and have successfully transplanted 3D-printed tissues loaded with primary liver cells into mice with chronic liver injury.

"The liver is especially interesting because it performs 500 functions – second only to the brain," Stevens said. "The liver's complexity means there is currently no machine or therapy that can replace all its functions when it fails. Bioprinted human organs might someday supply that therapy."

There are currently around 6,000 people waiting for organ transplants in the UK alone. Bioprinted organs could not only help meet this need but, as they can be printed using a patient's own cells, they could also greatly reduce the possibility of organ rejection. "We envision bioprinting becoming a major component of medicine within the next two decades," Miller said. **SF**

by JASON GOODYER
Jason is BBC Science Focus Magazine's commissioning editor.

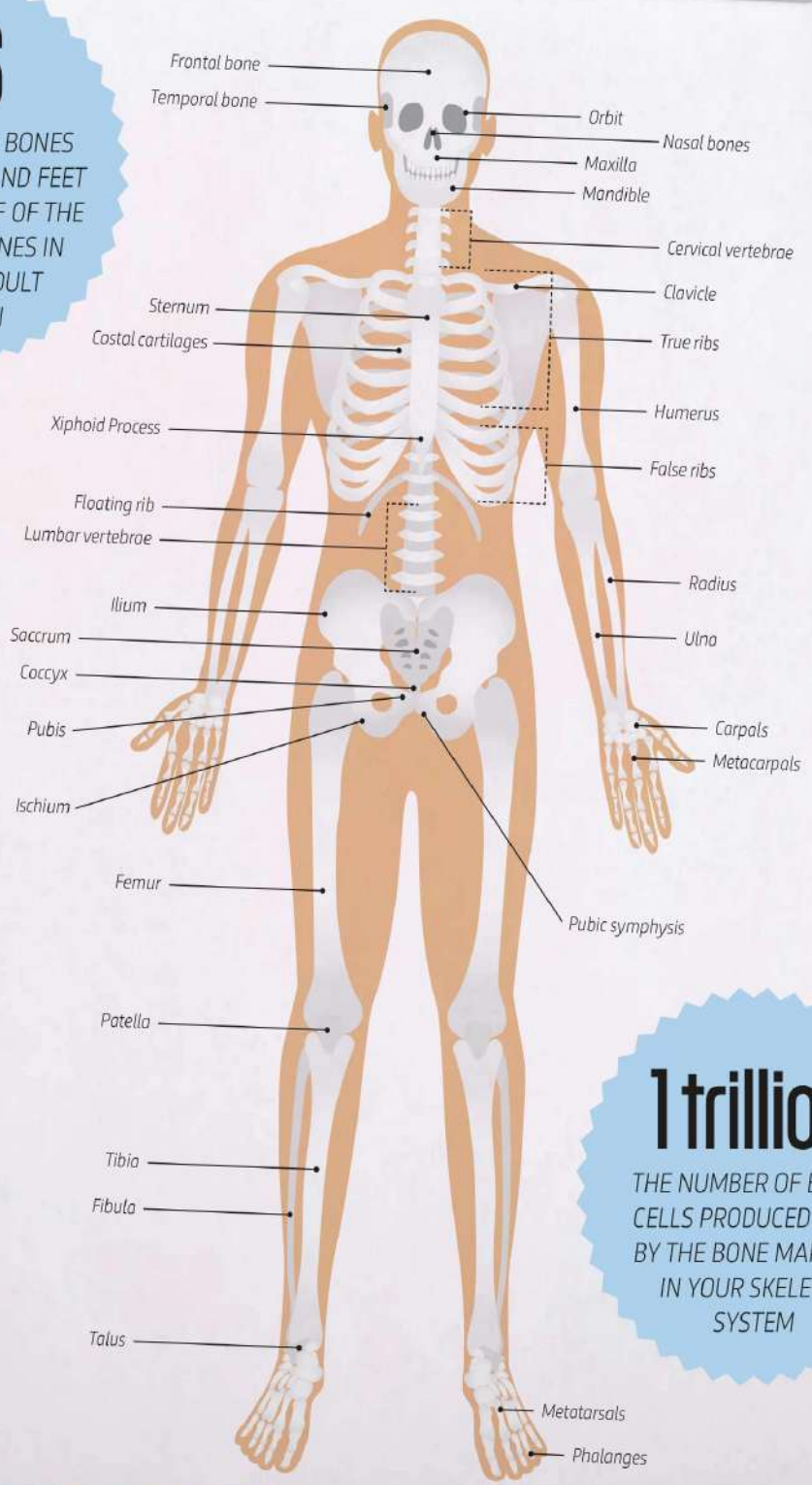
Skeletal SYSTEM

The bones in your skeleton work with your muscles to let you stand, walk, run, dance, jump and climb, as well as all the other movements you need your body to make, from getting out of bed, to lifting food to your mouth. But your skeleton does more than merely provide support and enable movement. It's also responsible for producing the red blood cells that carry oxygen around your body and may also have a role in metabolic regulation

GETTY IMAGES X2, VECTORSTOCK

106

THE NUMBER OF BONES IN YOUR HANDS AND FEET – JUST OVER HALF OF THE NUMBER OF BONES IN AN ENTIRE ADULT SKELETON



1 trillion

THE NUMBER OF BLOOD CELLS PRODUCED DAILY BY THE BONE MARROW IN YOUR SKELETAL SYSTEM


YOUR

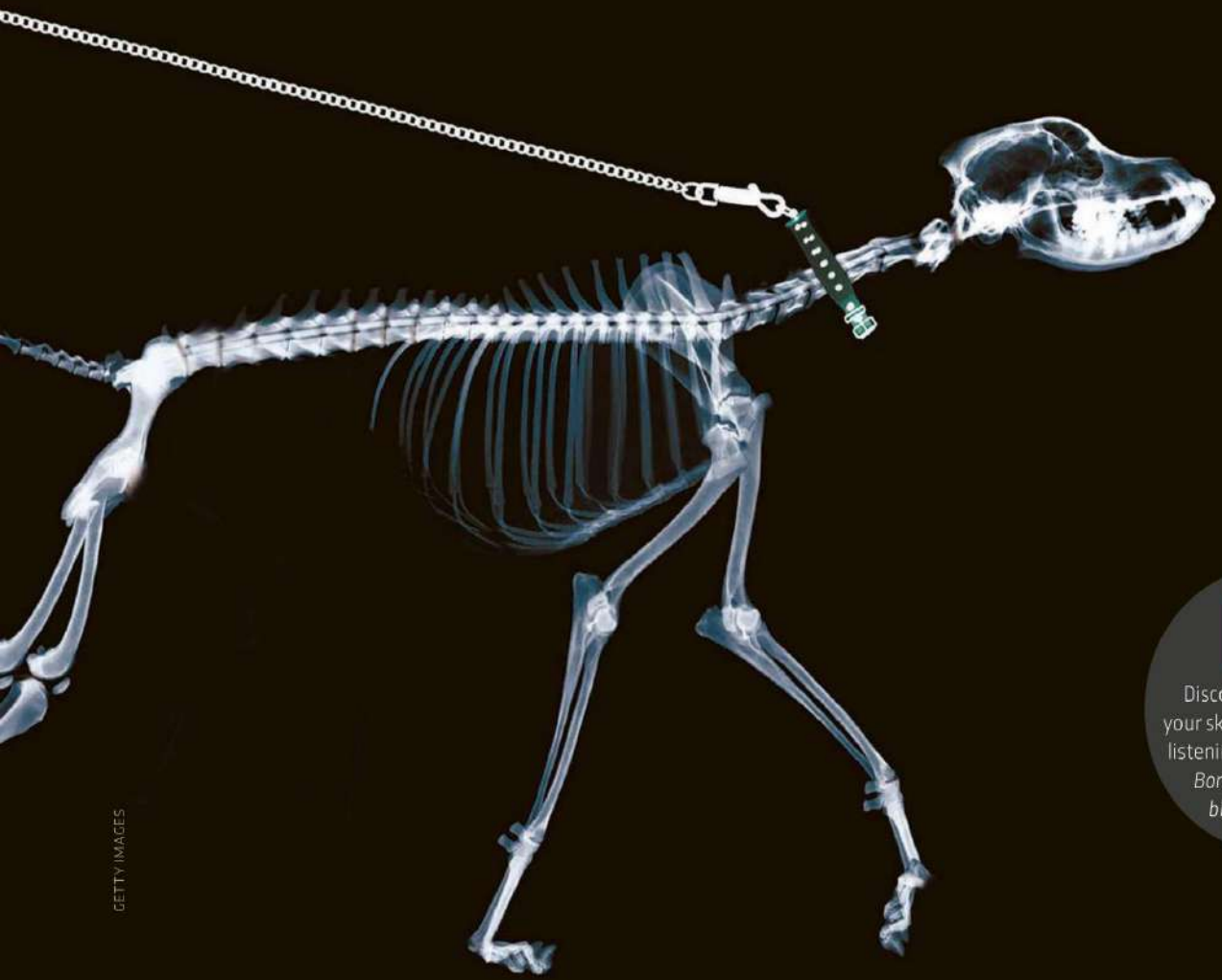
SUPPORT STRUCTURE

An internal scaffold of 206 bones, your skeleton is what holds your body up and enables you to move. But as researchers have recently discovered, that's far from all it does...

words by ALLA KATSNELSON

Bones: for most of us, they're just... there. It's easy to take them for granted as simply the scaffolding that holds up your body and gives it shape but the skeletal system is no sluggish stack of bones. For one thing, it's highly dynamic, fully rebuilding itself every decade or so. For another, it has a surprisingly diverse set of functions, some of which scientists have only recently begun to figure out. On top of its structural role, it also gives tension to your muscles, allowing you to move; stores calcium, phosphate and other minerals; makes blood cells to the tune of one trillion per day; and communicates with many different hormones to control calcium levels in different cells and to regulate your body's overall energy metabolism.

Animals like us, who have an internal skeleton, or endoskeleton, are in the minority. Insects, for example – the most numerous creatures on Earth – have exoskeletons made from a strong, fibrous substance called chitin that encase their bodies. Jellyfish have hydrostatic skeletons, ➲



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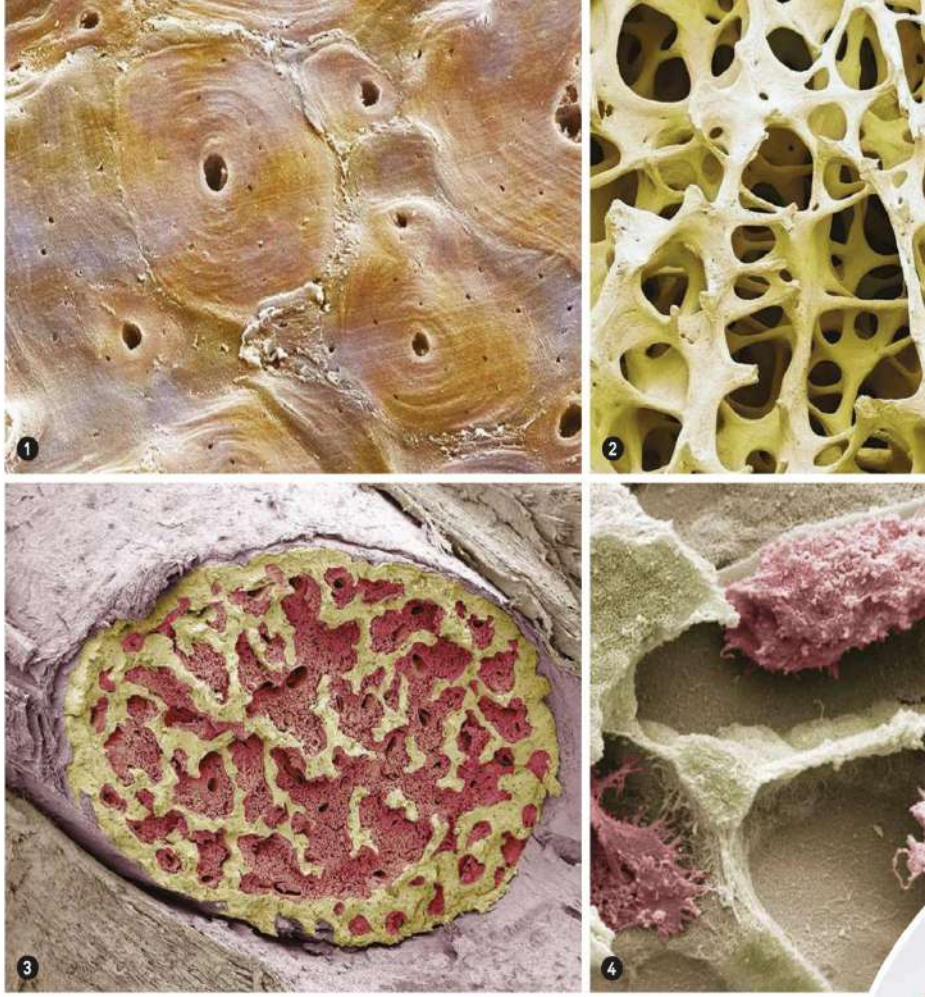
BBC WORLD SERVICE

Discover more about your skeletal structure by listening to *You and Your Bones and Muscles* bbc.in/2LZLdFR



which consist of a network of fluid-filled cavities and molluscs have shells.

The vertebrate skeleton is different because bones consist not of inert material but of living tissue, packed with blood vessels and different types of cells. What's more, the evolution of the endoskeleton has been a boon for vertebrates because it allows us to carry more body mass and grow larger. An elephant-sized beetle, or even a feline-sized one, would be a biomechanical impossibility – and thank goodness!

HEADS, SHOULDERS, KNEES AND TOES...

At birth, human skeletons contain 300 parts, some bone and some cartilage. As they grow, some of the bones fuse (particularly in the skull) and some of the cartilage (the kneecaps, for example) hardens to bone. In its adult form, the human skeleton has 206 bones – 106 of them in the hands and feet. All of them serve a purpose. "No bone is without its really major importance," says Dr Barbara Bergin, an orthopaedic surgeon in Austin, Texas.

The longest and strongest is the femur, which extends from the hip to the knee; the smallest is the stapes, a stirrup-shaped bone in your inner ear that transmits sound vibrations. Just one human bone, the hyoid, is unconnected to any others. It sits in the neck, below your chin, and anchors your tongue to help you swallow and produce the sounds needed for speech.

Your bones and joints give your body a wide range of motion. Bones also help propel you by acting as levers and providing tension against which your muscles can contract. Without the kneecap, for example, which serves as a fulcrum that allows you to straighten your knee, the quadriceps muscle, which runs along the femur, would lose much of its power. Two pea-shaped bones at the base of the big toe serve a similar function, carrying your entire body weight and allowing you to push off from the ground when you take a step. Lacking them can make walking difficult, which might be why the ancient Egyptians created artificial big toes, thought to be the first prosthetic body parts ever used.

Bones need to be strong, to support your weight, and flexible, so that they don't break too easily. A protein called collagen, which makes up about two thirds of the bone matrix, provides flexibility, while calcium and phosphate, which make up the rest, gives strength. This matrix forms two kinds of bone material. The bulk of it is compact bone, which is hard exteriors of your bones. Spongy bone – which is porous, but not soft like a sponge – sits on the inside.

Two pea-shaped bones at the base of your big toe carry your entire body weight and allow you to push off from the ground when you take a step

Osteoclasts and osteoblasts, cells that break bone down and build it up respectively, work within the bone matrix to run a continual process called bone remodelling. Microfractures, that accumulate in bone through normal daily activity, are sensed by osteoclasts, which then excavate the injured sites; shortly after, osteoblasts arrive to fill in the holes with down fresh bone matrix.

A third type of bone cells called osteocytes live within the bone and are thought to coordinate this process. Meanwhile, osteoclasts also receive signals from hormones in the bloodstream telling them to release calcium from the bones

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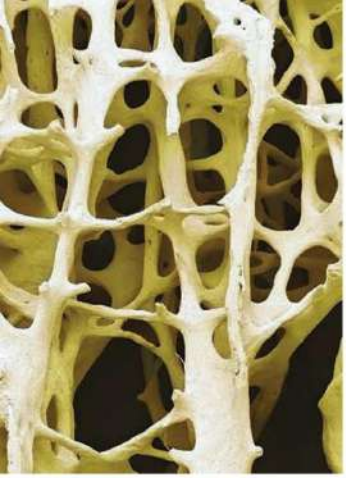


so that it can be used by muscles, nerves and other cell processes.

Until about 15 or 20 years ago, most scientists who studied the skeleton focused on its structural role and mineral exchange properties. But a couple of research teams that were experimenting on mice found that bone cells communicate with systems that regulate metabolic process, such as insulin regulation of glucose metabolism.

Thomas Clemens, professor of orthopaedic surgery at Johns Hopkins University in Baltimore, speculates that the skeleton could be a master regulator of energy use in the body. Researchers still aren't sure about that, but most are convinced of bone's new-found role. "Now it's pretty well recognised that bone is a metabolic organ," Prof Clemens says.

TIRED OLD BONES

As children grow, hormone signals instruct their bones to grow longer and denser. Girls achieve about 90 per cent of their bone mass by age 18 or so, and boys a couple of years later. Then, it's all downhill from about the age of 25. Bone mass gradually declines until middle age; the downward slope continues for men, but when women hit menopause, it plummets by about two to three per cent per year. (Astronauts who spend long periods in space lose that amount per month.)

Another key skeletal difference between men and women is pelvis size. The larger pelvis in women is associated with an internal rotation of the femur, which "creates a mechanical difference in our lower extremities," says Dr Bergin. This makes women more prone to injuries, such as anterior cruciate ligament tears. She recommends that women sit and jump like men – with their feet wide apart and knees rotated slightly outward – to limit the injury-causing stress on their bodies.

Protecting the skeleton is paramount to an active life. "Because of the advances in medicine, we are going to live an increasingly larger part of our lives in old age. So it's critical that we take care of our skeletons so we can live happy and pain-free." **SF**

1. A close-up of compact bone, which forms a bone's hard exterior

2. Spongy bone, the porous interior of a bone, is where the marrow is found and red blood cells are formed

3. Marrow (in red) can be seen in the cavities of the spongy bone in this coloured image of a broken finger

4. Osteoclasts in the process of bone remodelling

5. A prosthesic big toe, believed to have been made by the ancient Egyptians

GET PLASTERED

Plaster casts aren't the only way to help broken bones mend

Doctors have used plaster casts to set broken bones since the start of the 19th century. Casts are still the best approach for breaks in which the broken ends line up without too much fuss. These days, however, orthopaedic surgeons often opt for fibreglass over plaster because it's lighter, less messy and, in some cases, can get wet. Alternatively, a brace or splint may be enough to hold the bone in place for healing.

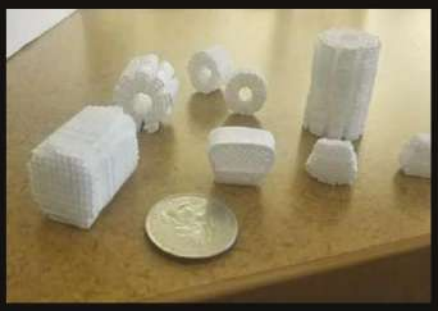
More complicated breaks may require internal fixation – surgically implanted screws, plates, rods or pins to hold bones together. These are generally made from stainless steel or titanium and often remain in place after the bone heals. Rods are especially useful for treating fractures in long bones such as the femur and the tibia. Pins, generally inserted through the skin, are helpful for breaks in smaller bones, such as those in the hand or wrist.

For breaks caused by traumatic injuries – particularly for open fractures or when tissue surrounding the break is damaged – orthopaedic surgeons might turn to external fixation to stabilise the bone. This method is also sometimes used to reset bones that didn't mend properly using simpler methods. Here, pins are surgically inserted into the bone through the skin on both sides of a fracture and attached to an external frame. The structure allows the surgeon to tweak the bone's position for proper alignment.

BREAKTHROUGHS

Build a better bone

3D-printed bone may offer an alternative to metal skeletal implants



Bone is one of the few tissues that can regenerate, so most fractures heal nicely. But in some cases – more serious breaks, for example, or bone loss or deformity caused by diseases such as cancer, accidents and other traumatic injuries – the body needs help rebuilding bone. A handful of researchers are working to create materials that can be placed directly into damaged areas to provide structural support and eventually get absorbed by the body as new bone forms.

Traditionally, orthopaedic surgeons in these cases have used metal implants – a material that doesn't quite gel with the body. "The problem is, we don't get tight integration of the bone to the implant, simply because it's metal," says Hala Zreiqat, professor of biomedical engineering at the University of Sydney. Instead, she looked to ceramic to create an artificial material that is, like bone, both highly porous and extremely strong.

She and her colleagues made a ceramic-based scaffold infused with zinc, strontium and other substances to bolster its biological and mechanical strength. They also developed the technology for producing it using a 3D printer. When they tested the material in sheep tibia bones, which are relatively close to the size of human tibias, they found that the material not only spurred native bone formation and fixed bone defects, but was also fully integrated within a year.

The material is being developed by an Australian company called Allegra Orthopaedics. It's on track for testing in humans in 2020, after another round of animal tests, Prof Zreiqat says. She envisions being able to print material based on a patient's CT scan, so as to tailor it precisely to their injury. Eventually Prof Zreiqat plans to test whether her material can replace a whole mandible of the jaw. "It's beautiful," she says. "The idea is, we can get enough bone growth and the doctors don't have to go back in."

ABOVE LEFT: The porous structure of bioceramic bone allows it to fuse more effectively with a patient's existing bone

TOP: Examples of the shapes and structures that can be made by using bioceramic bone and 3D-printing technology

ABOVE: The internal structure of bioceramic bone allows it to be both strong and light

by ALLA KATSNELSON (@lalakat) *Alla is science writer who specialises in biology, health, medicine and technology.*

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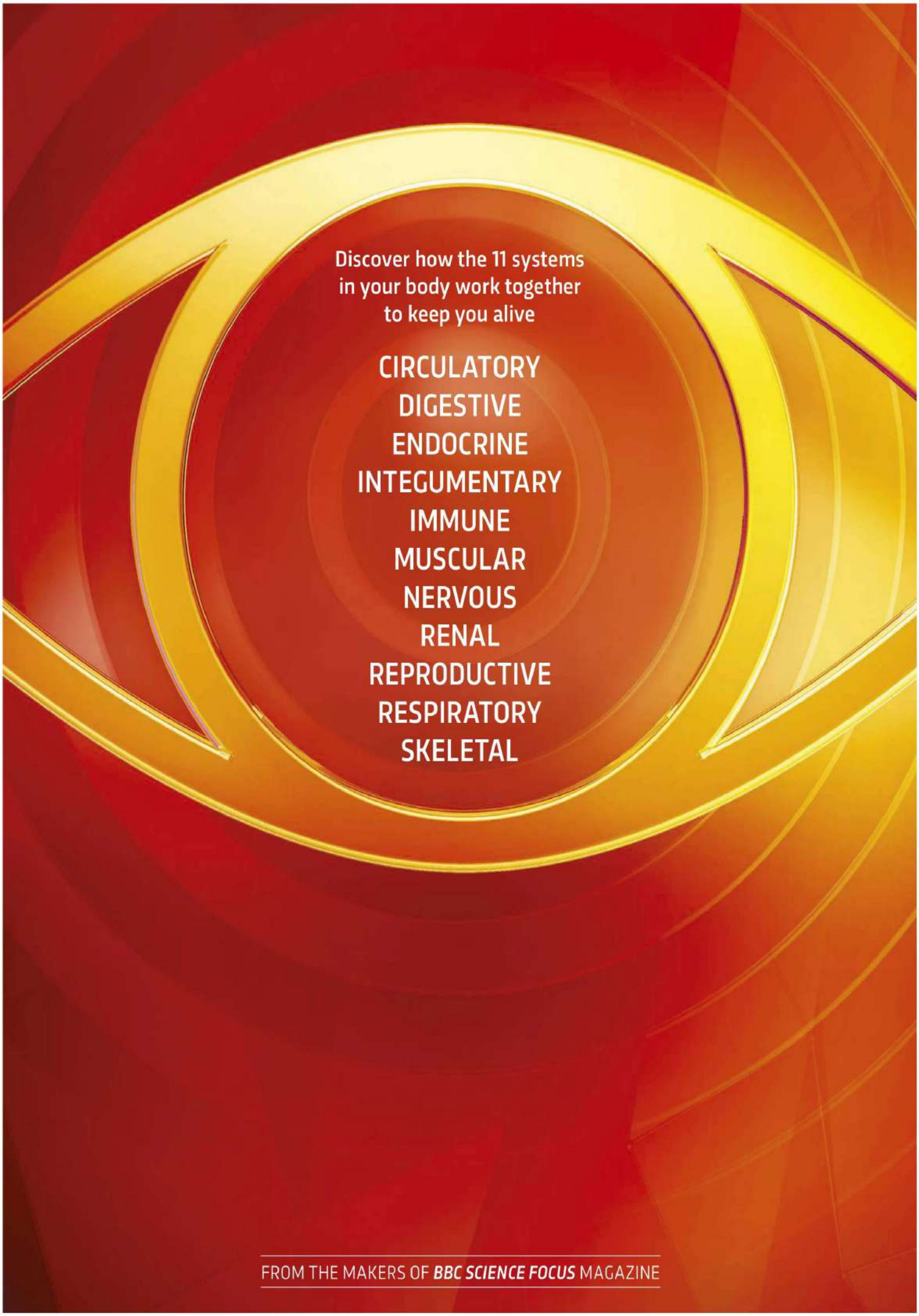
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